AHRQ Comparative Effectiveness Review Surveillance Program

CER # 16:

Comparative Effectiveness of Lipid-Modifying Agents

Original release date:
September 1st, 2009

Surveillance Report:
December, 2011

Key Findings:

- KQ1 is out of date
- KQ2 is possibly out of date
- KQ3 is possibly out of date
- Expert opinion: One of the 3 experts stated that the conclusions for KQ1-3 was not still valid
- There are 8 new FDA alerts

Summary Decision:

This CER's priority for updating is **High**

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1. Introduction

The purpose of this mini-report was to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether or not the CER No. 16 (Comparative Effectiveness of Lipid-Modifying Agents)[1] is in need of updating. This CER was originally released in Septemeber, 2009. It was therefore due for a surveillance assessment in December, 2010. When the Surveillance program began in the summer of 2011, this CER was selected to be in the first wave of reports to go through the assessment.

This CER included 101 unique trials identified by using searches through August, 2008 and addressed three key questions to compares the benefits and risks of two treatment options (increasing the dose of a statin or using a statin in combination with a lipid-modifying agent of another class) in terms of clinical events (e.g., myocardial infarction, stroke, or death), surrogate measures (e.g., levels of LDL-c), tolerability, and adherence. The key questions of the original CER were as the following:

1. For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?

2. Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

3. Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

The conclusion(s) for each key question are found in the executive summary of the CER report.[1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The Food and Drug Administration (FDA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, FDA surveillance alerts), a consensus-based conclusion was drawn whether or not any given conclusion warrants any updating (up to date, possibly/probably out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere. [2-4].

2.1 Literature Searches

The CER search strategies were reconstructed in Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), Embase and Cochrane Central Registry of Controlled Trials (CENTRAL) as per the original search strategies appearing in the CER's Appendix A.[1] All searches were limited to 2008 to present (October 27 2011). The Cochrane update was run on the Wiley platform as the OVID platform was not available through our institutional subscription. The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were applied according to the databases indicated in the appendix and in the search strategy section of the CER report. The MEDLINE search was limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and several specialty journals (American Journal of Cardiology, Circulation, Atherosclerosis, Clinical Chemistry, and Current Medical Research & Opinion). Restricting by journal title was not possible in the Cochrane search and pertinent citations were instead selected from the results. Study design filters were not applied to the Cochrane search since the Cochrane Central Register only contains randomized or controlled clinical trials. Additional search strategies were implemented in Medline and Embase (according the above dates) to identify harms research and another in Medline with the RCT filter turned off. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as one described in the original CER[1].

2.3 Expert Opinion

In total, 4 experts (2 CER-specific and 2 other) were requested to provide their feedback in a provided their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only. For any given CER that included a meta-analysis, the assessment started with the identification of qualitative signal(s), and if no qualitative signal was found, this assessment extended to identify any quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might be in need of updating. The definition and categories of updating signals are presented in Appendix B and publications.[2,4]

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and FDA surveillance alerts) was collated and summarized. Taken into consideration the totality of evidence (i.e., updating signals, expert opinion, and FDA surveillance alerts) presented in a tabular form, a conclusion was drawn whether or not any conclusion(s) of the CER warrant(s) updating.

Conclusions were drawn based on four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.

- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.

- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determination of priority groups (i.e., Low, Medium, and High) for updating any given CER was based on two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?

- How out of date are the conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

A total of 1170 bibliographic records were identified (MEDLINE=632, Embase=472, and CENTRAL =66). After de-duping, 565 records remained (MEDLINE=380, Embase=179, and CENTRAL =6), of which 148 records were deemed potentially eligible for full text screening. Of the 148 full text records, 19 were included in the update.[5-23] We also included one pivotal trial that was identified through an FDA alert. [24] Thus, a total of 20 reports were included in this report.[5-24]

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

The study, population, treatment characteristics, and results for the 20 included publications are presented in Appendix C (Evidence Table).

One of the 20 included publications represented a systematic review and meta analysis of randomized trials, 17 [5-7,9-12,14-22,24] were randomized controlled trials (RCTs) and 2 were observational studies (cohort design).[13,23] The length of the follow-up across majority of the studies ranged from 6 weeks [6,7,11,14] to 12 weeks[10,17,20,21] . The longest follow-up period was 4.7 years.[15].

The number of participants included in the randomized trials ranged from 15[6] to 5,518.[15] The sample size of the observational studies ranged from 187[13] to 584,784 participants.[23]

The population was consisted of individuals requiring intensive lipid therapy in 12[5-9,14-16,18,20,21,24] of the 20 included reports, and all risk groups in the remaining 8 studies.[10-13,17,19,22,23]

Of the included 20 studies, 10 compared ezetimibe plus statin versus statin alone,[5-9,9-11,20,22 2,16,71,8,14,20,26,30,59,97] 8 compared fenofibric acid plus statin versus statin alone [12-18,21], 1 compared niacin extended release plus statin versus statin alone[15] and 1 compared omega-3 acid ethyl ester plus statin versus statin alone.[19] A total of 3 reports compared combination therapy to a higher dose of statin monotherapy, [7,11,20] and 17 compared combination therapy to any statin monotherapy .[5,6,8-10,12-19,21-24] Of the identified studies, 2 were relevant to Key question one[15,24], 18 were relevant to Key question two [5-14,17-24] and 5 were relevant to Key question three. [5,6,12,15,16]

Only 2 studies[15,24] reported the clinical outcomes such as fatal/nonfatal cardiovascular diseases events, nonfatal myocardial infaraction (MI), nonfatal stroke, ischemic stroke and coronary cerebral vascularization events, 19 studies[5-12,14-21,21-24] reported the levels for surrogate outcomes (e.g., LDL-c, LDL-c goal attainment, HDL-c, TC/HDL-c ratio), and 8 studies[7,12,13,15-17,20,22,24] reported harms such as rhabdomyolysis, serious adverse events (SAEs), aspartate

amynotransferase (AST) ≥3 times Upper Limit of Normal (ULN), alanine transaminase (ALT) ≥3 x ULN, creatine phosphokinase (CPK) ≥10 x ULN, myalgia, and tolerability.

3.2.2 Qualitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

Key question #1

Comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy

Long-Term Benefits and Serious Adverse Events: The lack of evidence on clinical outcomes of interest such as MI, stroke, or death was supplemented by two identified pivotal trials in the update search. [15,24] **1 Signal (A 6)**

All-cause mortality

1. Statain + fibrates vs. statin monotherapy: The insufficient evidence in the original CER was supplemented by a randomized pavitol clinical trial [15] with HR: 0.91 and 95% CI: 0.75, 1.10; p=0.33. **1 Signal (A 6)**

2. Statain + niacin extended dose release vs. statin monotherapy:The less precise effect estimate in the orginal CER was supplemented with a more precise effect estimate via a pivotal clinical trial[24] with HR:1.16, 95% CI: 0.87, 1.56; p=0.3. **1 Signal (Other)**

Vascular death

1. Statin plus niacin vs. statin montherpay: The lack of evidence in the original CER was supplemented through a pivotal clinical trial [24] with HR: 1.17, 95%CI: 0.76, 1.80; P=0.47. **1 Signal (A 6)**

2. Statin plus fibrates vs. statin montherpay: There was no evidence in the original CER; however, it was supplemented by a pivotal trial [15] with HR: 0.86, 95% CI: 0.66, 1.12; p=0.26. **1 Signal (A 6)**

3. No evidence for this outcome in a high-risk population and compared the combination to a higher statin dose was identified. **No Signal**

Non fatal MI

1. Statin plus niacin vs. Statin montherapy: Lack of evidence in the original CER was supplemented by a pivotal trial[24] with: HR 1.11, 95%CI: 0.84, 1.47; P=0.46. **1 Signal (A 6)**

2. Statin plus fibrates vs. Statin montherapy: No event was reported in either groups in the original CER; however, in the update search a pivotal trial [15] reported the non fatal MI with HR: 0.91, 95% CI: 0.74, 1.12; p=0.39. **1 Signal (A 6)**

Ischemic Stroke: (statin plus niacin vs. statin montherpay): The lacks of evidence in the original CER was supplemented through a pivotal trial [24] demonstrating HR 1.61, 95%CI: 0.89, 2.90; P=0.11. **1 Signal (A 6)**

Any or unspecified stroke: (Statin plus fibrates vs. Statin montherapy): There was no evidence on any or unspecified stroke in the original CER but the update search identified a pivotal trial [15] reporting HR: 1.05, 95% CI: 0.71, 1.56; p=0.80. **1 Signal (A 6)**

Serious adverse events

1. **(**population requiring intensive lipid therapy) The lack of evidence on SAEs among population requiring intensive lipid therapy in the original CER was supplemented by a clinical trial [20] SAE [n (%)]: **1**5 (3%) vs. 14 (3%)
   SAE (drug related): 1 (<1%) vs. 0**. 1 Signal (A 6)**

However, the findings from 2 clinical trials [7,22] in (statin plus ezetimibe combination vs. statin higher dose monotherapy) was in agreement with the original CER demonstrating no significant difference between groups and the data from one clinical trial [12] in (Fenofebric acid + low dose statin vs. low dose statin) did not present enough data. **No Signals**

Cancer: No new evidence was found in the update search. **No Signal**

Key Question # 2

Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?

Participants attaining ATP III LDL-c goals

1. Statin plus ezetimibe vs. statin monotherapy in all trial population: The findings from a non RCT study [23] was in conflict with the original CER demonstrating higher LDL-c goal attainment for the monotherapy group: 58.4% vs. 81.4%; p<0.01 based on the year 2011, and 46.4% vs. 31.5%; p<0.01 according to year 2004 definition of the ATP III LDL-c goal attainment. **1 Signal (Other)**

However, the findings from two clinical trials[8,17] were in agreement with the original CER favoring combination therapy over monotherapy in (statin plus ezetimibe vs. statin monotherapy in population requiring intensive lipid therapy) and in (statin plus fibrate vs. statin monotherapy) respectively. **No Signal**

LDL-c percentage means change from baseline (mg/dl)

The findings from 10 clinical trials [5-11,17,18,22] were in agreement with the original CER mostly favoring the combination therapy. **No Signal**

However, the findings from the following studies were in conflict with the original CER:

1. Statin +Ezemitib vs. Statin, in all trial poulation: A non-RCT (retrospective) study [23] favored the monotherapy over the combination therapy. The Least-squares mean % change in LDL-C from baseline was -35 vs. -46.7; p<0.001. **1 Signal (Other)**

1. Statin +fibrate vs. Statin in all trial population: A clinical tiral [12] demonstrated almost comparable LDL-c levels in both groups: The LDL-c level reduction was (37% vs. 36%). **1 Signal (A 6)**

2. Statin +fibrate vs. Statin in population requiring intensive lipid therapy: A statistically non-significant finding from the original CER was in conflict with a statistically significant one from a clinical trial [21] favoring the combination therapy. The baseline vs. 12 months LDL-c levels were: (188±17 vs.184±19) vs. (112±14 vs. 142±17); p<0.001. **1 Signal (A 6)**

HDL-c level change from baseline (mg/dl)

1. Statin lower dose +Ezetimibe vs. Statin higher dose in population requiring intensive lipid therapy: The original CER lacks evidence on HDL-c in the stated population and treatment dose; however, the findings from 2 clinical trials [7,20] reported HDL-c mean percentage change as follows:

    a. 2%, 95% CI: 0.3, 4; p=0.021 at 6 weeks and 3%, 95% CI: 2,5;p< 0.001 at 12 weeks.[20] **1 Signal (A 6)**

    b. -4.5%; p=0.017 when receiving statin 10mg in monotherapy group and -0.3;p=NR when receiving statin 20mg in monotherapy arm.[7] **1 Signal (A 6)**

2. Statin +Ezetimibe vs. Statin in population requiring intensive lipid therapy: In conflict with the original CER, the findings from a clinical trial [18] did not favor combination therapy with HDL-c levels at the baseline 37±8 vs. 37±8; p=NS and 38±7 vs. 37±9; p=NS at the final follow up. **1 Signal (A 6)**

Similarly, the findings from another clinical trial[5] did not favor the combination therapy and there was a slight reduction in the HDL-c level from baseline to final follow up: 1) at Baseline: (48±4) vs. (45±4); p=NR; 2) at year 1: (42±3) vs. (46±3); p =NR, and 3) at year 2: (46±3) vs. (44 ±4);p=NR. **1 Signal (A 6)**

The findings from another clinical trial [14] also did not favor combination therapy as in the combination arm the HDL-c levels did not change from baseline vs. week 6 (48±13 vs. 48±13;

p=0.006) but there was a slight change from baseline to week 6 in the monothrapy arm (45±13 vs. 46±11; p=NR). **1 Signal (A 6)**

3. Statin +niacin vs. Statin: Insufficient evidence in the original CER was supplemented by a clinical trial [24] favoring the combination therapy as the mean HDL –c increased from 34.8±5.9 at the baseline to 44.1±11.3 at the final follow up in combination group and from 35.3±5.9 at the baseline to 39.1±7.7 at the final follow up in the monotherapy group. **1 Signal (A 6)**

The findings from the following reports were in agreement with the original CER: 1) In (Statin +Ezetimibe vs. Statin in all trial population) five clinical trials [6,9-11,22] demonstrated inconsistent results for HDL-c levels, and 2) In (Statin +Omega-3 vs. Statin, in all trial population) one trial [19], in (Statin +Fibrate vs. Statin, in all trial population) another clinical trial [12] , and in (Statin +Fibrate vs. Statin in population requiring intensive lipid therapy) one study [21] favored combination therapy over monotherapy . **No Signal**

Total cholesterol: HDL-c ratio (mg/dl)

The findings from the following studies were in agreement with the original CER favoring the combination therapy over monotherapy: 1) In (Statin lower dose +Ezetimibe vs. Statin higher dose in population requiring intensive lipid therapy) two clinical trials [7,20], and 2) In (Statin +Ezetimibe vs. Statin in population requiring intensive lipid therapy) four identified studies [8,10,11,22]. **No Signal**

Measures of atherosclerosis

In conflict with the original CER, the finding from a clinical trial [5] demonstrated that in statin-naïve patients Statin initiation with or without ezetimibe halted progression of peripheral atherosclerosis. However, the peripheral atherosclerosis progressed when ezetimibe was added to patients previously on statins. The study concluded that ezetimibe's effect on peripheral atherosclerosis may depend upon relative timing of statin therapy. **1 Signal (A 6)**

Adherence and harm

<u>Elevated AST & ALT ≥ 3 times upper limit of normal (ULN)</u>

The findings from 2 clinical trials [7,20] were in agreement with the original CER demonstrating no statistically significant difference between the combination versus monotheapy groups in (Statin lower dose +Ezetimibe vs. Statin higher dose in population requiring intensive lipid therapy) and (Statin +Ezetimibe vs. Statin in all trial population). **No Signal**

However, the findings from another clinical trial[22] was in conflict with the original CER results for AST≥ 3times ULN showing a significant difference for AST between the groups. [Statin vs. Statin +Ezemitibe: n(%); Difference (95%CI)]: 1) ALT ≥ 3ULN: 2 (0.3%) vs. 1 (0.2%); -0.1 (-

0.9, 1.0); p=0.81; 2) AST≥ 3ULN: 1 (0.2%) vs. 5 (1.1%); 1.0 (0.1, 2.5); p=0.03; and CPK≥ 10ULN: 0 vs. 1 (0.2%); 0.2 (-0.4,1.3); p=0.22. **1 Signal (A 6)**

AST & ALT ≥ 3 times ULN, creatinine phosphokinase (CPK), and Discontinuation

The findings from 4 clinical trials [12,15,17,24] were in agreement with the original CER in (Statin +Fibrate vs. Statin in all trial population) and no evidence was identified on (Statin +BAS vs. Statin): **No Signal**

However, two studies [13,15] presented conflicting results to the original CER demonstrating patients developing rhabdomyolysis:

a. Statin +fenofibrate vs. statin: Adjusted IRR=3.75, 95% CI: 1.23–11.40. **1 Signal (A 6)**

b. The n (%) was 4 (0.1) vs. 3 (0.1); p= 1.00. **1 Signal (A 6)**

Key Question# 3

Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?

Participants with diabetes mellitus:

1. Any relevant outcome:

No evidence was found on: 1) lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy, and 2) across various statin doses in combination and monotherapy in statin-niacin, statin-BAS, and statin-omega-3 combinations. **No Signal**

2. LDL-c and HDL-c level changes from baseline (mg/dl):

Findings from 2 clinical trials [6,15] were in agreement with the original CER favoring combination therapy in (Statin-ezetimibe vs. statin) and (Fenofibrate +statin vs. statin). **No Signal**

However, the findings from another clinical trial[16] was in conflict with the original CER showing no significant difference in median HDL-c in combination therapy and a significant reduction in monotherapy group. (Baseline: 38 vs. 40) vs. (1 year: 38 vs.39); p=0.002. And a non- significant difference among the groups for median LDL-c: (Baseline vs. 4 year: 93 vs. 78) vs. (Baseline vs. 4 year: 93 vs. 78);p=0.68. **1 Signal (A 6)**

3. All-cause mortality

Statin + fibrates vs. statin monotherapy: The evidence in the original CER is supplemented by calculation of effect estimate and 95% CI via a randomized clinical trial [15] in which HR: 0.91 and 95% CI: 0.75, 1.10; p=0.33. **1 Signal (A 6)**

4. Vascular death

Statin plus fibrates vs. statin montherpay: The lack of evidence in the original CER was supplemented by a pivotal trial [15] with HR: 0.86, 95% CI: 0.66, 1.12; p=0.26. **1 Signal (A 6)**

5. Non fatal MI

Statin plus fibrates vs. Statin montherapy: No event was reported in either groups in the original CER but a pivotal trial [15] reported the non fatal MI with HR: 0.91, 95% CI: 0.74, 1.12; p=0.39. **1 Signal (A 6)**

6. Ischemic Stroke:

Any or unspecified stroke (Statin plus fibrates vs. Statin montherapy): There was no evidence on any or unspecified stroke in the original CER but an identified pivotal trial [15] demonstrated HR: 1.05, 95% CI: 0.71, 1.56; p=0.80. **1 Signal (A 6)**

Women:

The lack of evidence in women subgroup was supplemented by a clinical trial [12] that present data on HDL, LDL, TC/HDL ratio and adverse events (e.g. serious, drug related, ALT, AST and CPK levels) in combination therapy (Fenofebric acid + statin) verusrus (statin) monotherapy. **8 Signals (A 6)**

Participants with established vascular disease:

The lack of evidence in the original CER was supplemented by a clinical trial [5] demonstrating data on HDL, LDL and plaques. **3 Signals (A 6)**

Participants of 80 years of age or older, participants of African descent, Participants with baseline LDL-c of 190 mg/dL or above, participants of Asian descent, and Hispanics: No evidence. **No Signal**

3.2.3 Quantitative signals

See also Table 1 (Summary Table), Appendix B, and Evidence Table (Appendix C)

The presence of quantitative signals (B1 and B2) was checked only if none of the studies identified through the update search indicated a qualitative signal.

3.3 FDA surveillance alerts

There were a total of **8** FDA alerts issued:

1. **Label Change:**

    a. Niacin extended realease/simvastatin.
    b. Niacin extended release/lovastatin.
    c. Ezetimib/Simvastatin: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis.
    d. Simvastatin: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis.
    e. Simvastatin: Myopathy/Rhabdomyolysis.

2. **Drug Safety Communication**
    a. Simvastatin: 80 mg should not be started in new patients, including patients already taking lower doses of the drug.
    b. Rosuvastatin calcium: Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Crestor. These risks can occur at any dose level, but are increased at the highest dose (40 mg).
    c. Fenofibric acid: the drug may not lower the risk of major cardiovascular events.

For further information on the FDA alerts, please refer to Appendix E.

3.4 Expert opinion

Three of the 4 contacted clinical experts (two CER-specifics and two other) provided their responses/feedback in the matrix table (Appendix D). The responses from the two experts were consistent in agreement that all three conclusions outlined in the executive summary of the CER were still valid. However, one expert's opinion was in conflict with the original CER findings indicating the study summery not to be still valid.He was aware of some publications that impact the findings.

4. Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, FDA surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the assessments, this CER is categorized in **High** priority group for updating.

Key Question # 1

Signals from studies identified through update search: the qualitative signal (10 signals) were met. **10 Signal (9 A 6 and 1 Other).**

Experts: One of the three experts stated that conclusions in the key question # 1 was not still valid.

FDA surveillance alerts: A total of 8 alerts were identified.

Conclusion: **10 of 15 conclusions are out of date.**

Key Question # 2

Signals from studies identified through update search: i) A total of 13 (and 1 other) qualitative signals were identified. **14 Signals (13 A 6 and 1 Other).**

Experts: One of the three experts stated that conclusions in the key question # 2 was not still valid.

FDA surveillance alerts: A total of 8 alerts were identified.

Conclusion: **14 of 48 conclusions are possibly out of date**

Key Question # 3

Signals from studies identified through update search: A total of 16 qualitative signals were identified. **16 Signals (A 6).**

Experts: One of the three experts stated that conclusions in the key question # 3 was not still valid.

FDA surveillance alerts: A total of 3 alerts were identified.

Conclusion: **16 of 25 conclusions are possibly out of date**

Summary Table (Lipids)

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		FDA/Health Canada surveillance alerts	Expert opinion (CER + local)	Conclusion on validity of CER conclusion(s)
		Qualitative	Quantitative			
Key Question 1. For patients who require intensive lipid-modifying therapy, what are the comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?						
Long-Term Benefits and Serious Adverse Events There are several important limitations in the evidence regarding long-term clinical outcomes. Most of the evidence originates from short-term studies aimed at biochemical measures and therefore is insufficient for the clinical events of interest, including the occurrence of MI, stroke, or death. In trials of combination therapy, the monotherapy comparator arms rarely explored higher-dose statins or were not performed in individuals requiring intensive lipid lowering. Due to these limitations in the available data, we present first our results based on the available evidence	**2 RCTs** [15,24]	**1 Signal (A 6)** Two RCTs (ACCORD-lipid and Aim -High) are pivotal trials with 4.7 years and 3 years follow up,and 5518 patients with diabetes and 3414 patients with CHD respectively. Both have assessed the clinical outcomes such as MI, Stroke, cardiovascular deaths.		8 FDA alerts	One expert stated that the conclusion is not still valid, :General Comment: There have been several new large trials published in this area since the report was written. They contribute significantly more data on both surrogate outcomes (lipid levels) and	Out of date

lowering when combination treatment is compared to a higher dose of a statin, and then provide a broader perspective using available data in all risk groups comparing combination therapy to any monotherapy statin dose.					outcomes including MI, stroke and death. In addition due to the large numbers of participants there is significantly more data on safety outcomes. In some instances the direction of the effect has not changed but the quantity and quality of the evidence significantly impacts on the precision of the conclusions. AIM-High comprised 3414 participants on simva +/- niacin clinical events and death were outcomes. Increase in	

					stroke seen in treatment group 2 experts stated that this conclusion is still valid. One expert has mentioned conclusions of four RCTs (not a personnel comment) of which 3 (Aim High , ACCORD lipid and ACCORD Eye) are already included in this report and 1 RCT (SHARP study -Lancet 2011;377:2181-2192) was excluded because it was not a comparative study (combination therapy vs. placebo only).	

All-cause mortality. The quality of evidence was very low for all available comparisons of combinations and monotherapy reported below. For individuals requiring intensive therapy, limited evidence was available for statin combinations with ezetimibe and fibrates compared to higher doses of statins. In the two statin-ezetimibe combination trials, no deaths occurred in either the combination or the statin monotherapy group, precluding a comparative analysis of mortality. A single trial with a statin-fibrate combination showed no difference in mortality compared with a higher dose statin. (Table 18: Three trials used the same statins in combination therapy and monotherapy, one with higher dose monotherapy. A significant difference was not observed among participants with mixed risk factors. These trials reported 3 deaths in 339 evaluable participants.) Trials comparing combination therapy with statin monotherapy that were not limited to individuals requiring intensive lipid lowering and did not necessarily compare combination	**1 RCT** [15]	**1 signal** Findings from ACCROD lipid trial (n=5518 diabetic patients; 4.7 yrs follow up) showed 221 events in the combination therapy and 203 events in monotherapy groups with HR: 0.91 and 95% CI (0.75, 1.10); p=0.33.		**2 FDA Notifications** 1) Drug Safety Communication: Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. 2)Label Change Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis -Diltiazem: Do not exceed 40 mg simvastatin daily -The combined use of simvastatin in patients receiving diltiazem should not exceed 40 mg daily unless the clinical benefit is likely to outweigh the increased risk of myopathy. - Cases of myopathy/rhabdomyolysis have been observed with	See above	See above

therapy with a higher dose of statin monotherapy were examined for an effect on mortality. No significant differences between treatments were observed across any combination, including statin-omega-3 combination, which was studied in three trials, one of which was a large trial lasting 5 years of 18,645 Asians. (Table 28: No significant difference was observed for the outcome in trials in mixed populations (OR 1.08; 95% CI 0.17, 6.72) or <u>in participants requiring intensive lipid lowering therapy (OR 1.84; CI 0.16, 20.76))</u>	**1 RCT[24]**	**1 signal** In Aim High trial (n= 3414 patients with CHD; 3 years follow up) there were 96 events in intervention and 82 event in control groups. The HR: 1.16, 95% CI (0.87, 1.56); p=0.3.		simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products.		
Vascular death. Treatments aimed at modifying lipids might be expected to lower the rates of death due to vascular diseases such as heart disease and stroke. However, no trials examined this outcome in a high-risk population and compared the combination to a higher statin dose. Across all available trial populations, two trials each of statin-ezetimibe and statin-niacin combinations did not demonstrate a difference in the occurrence of rare vascular deaths. The quality of evidence was very low for evidence pertaining to both combinations.	**No evidence**	**No Signal**		See above	See above	See above

Vascular death- Continued: (statin plus niacin vs. statin montherpay) Table 28: No significant difference was observed for the outcome in trials in mixed populations (OR 0.53; 95% CI 0.03, 8.64) or in participants requiring intensive lipid lowering therapy (no deaths occurred in either group. **(statin plus fibrates vs. statin montherpay)** **Table 18: No evidence**	**1 RCT**[24] **1 RCT** [15]	**1 Signal** Findings from Aim High trial (n= 3414 patients with CHD; 3 years follow up) showed 45 deaths in intervention group and 38 deaths in the control group due to all cardiovascular causes: HR 1.17, 95%CI (0.76, 1.80); P=0.47. **1 signal** Findings from ACCROD lipid trial (n=5518 diabetic patients; 4.7 yrs follow up) showed 114 deaths in the intervention group (n=2753) and 99 deaths in the control group (n=2765). HR: 0.86, 95% CI (0.66, 1.12); p=0.26.		**1 FDA Notification** (Safety communication) on fenofibric acid (Trilipix, Abbott), stating that the drug may not lower the risk of major cardiovascular events based on the ACCORD lipid trial.	See above	See above
Other clinical outcomes. For the outcomes of reduction of MI or stroke or avoidance of revascularization procedures on the carotid or coronary vessels, no evidence comparing combination therapy with a higher dose of statin was available. Evidence comparing various doses of statin-ezetimibe, statin-fibrate, statin-niacin, and statin-BAS combinations with statin monotherapy was available from few trials registering rare events, and no significant difference was detected. One large statin-omega-3 trial of 18,645 Asians demonstrated no significant difference between				**2 FDA Notifications** (Label Change) for: 1) Niacin extended realease/simvastatin, and 2) Niacin extended release/lovastatin Reproting the adverse events that were not the outcome of interest in this report.		

treatments for the outcomes of nonfatal MI, hemorrhagic stroke, ischemic stroke, and all stroke over a period of 5 years. **Other clinical outcomes in** Table 28: **(Statin plus niacin vs. Statin montherapy)** **Non fatal MI**: No evidence	**1 RCT** [24]	**1 Signal** Findings from Aim High trial (n= 3414 patients with CHD; 3 years follow up) showed 104 events in the combination therapy group (n=1718) and 93 events in the monotherapy group (n=1696) due to nonfatal MI: HR 1.11, 95%CI (0.84,1.47);P=0.46.				
Other clinical outcomes in Table 28- **Continued:** **Ischemic Stroke**: No evidence	**1 RCT**[24]	**1 Signal** Findings from Aim High trial (n= 3414 patients with CHD; 3 years follow up) showed 29 events in the intervention group (n=1718) and 18 events in the control group (n=1696) due to Ischemic Stroke: HR 1.61, 95%CI (0.89, 2.90);P=0.11.		See above	See above	See above
Other clinical outcomes- Continued: Table 18: **(Statin plus fibrates vs. Statin montherapy)** **Non fatal MI:** One trial compared combination therapy with same statin and same dose monotherapy in participants with diabetes mellitus. No events were reported. This trial	**1 RCT**[15]	**1 signal** Findings from ACCROD lipid trial (n=5518 diabetic patients; 4.7 yrs follow up) showed 186 events in the intervention group (n=2753) and 173 events in the control group (n=2765) due		**1 FDA Notification** (Safety communication) on fenofibric acid (Trilipix, Abbott), stating that the drug may not lower the risk of major		

reported no events in 48 evaluable participants.		to Non fatal MI. HR: 0.91, 95% CI (0.74, 1.12); p=0.39.		cardiovascular events based on the ACCORD lipid trial.		
Other clinical outcomes- Continued: **Any or unspecified stroke :No evidence**	**1 RCT**[15]	**1 signal** Findings from ACCROD trial (n=5518 diabetic patients; 4.7 yrs follow up) shows that there were 48 events in the combination therapy group (n=2753) and 51 events in the monotherapy group (n=2765) due to any stroke. HR: 1.05, 95% CI (0.71, 1.56); p=0.80.		See above	See above	See above
Serious adverse events. The quality of evidence was very low for all available combination and monotherapy comparisons. Evidence pertained to all available trial populations and not specifically those in need of intensive treatment.	**1 RCT** [20]	**1 Signal** In population requiring intensive therapy Atrovastatin 10+ Ezetimib vs. Atrovastatin20,40 <u>Adverse Event; n (%)</u> Serious: 15 (3%) vs. 14 (3%) Serious drug related: 1 (<1%) vs. 0		See above	See above	See above
Serious adverse events- continued: Evidence comparing a combination with a higher dose of statin	**1 RCT** [22]	**No Signal** <u>Adverse events:</u>		**2 FDA Notifications** 1) On Ezetimib/	See above	See above

monotherapy was available only for the statin-ezetimibe combination. Three trials with a maximum duration of 24 weeks demonstrated no difference in the rate of serious adverse events. Overall, 5 percent of participants had an event. When various doses and statin types in combinations were compared with statin monotherapy, no significant differences were noted across all combinations, including evidence that combined 27 statin-ezetimibe trials with over 13,000 participants. Absolute rates of serious adverse events varied between 2 and 4 percent. Even across all combinations, no differences were detected when analyses were restricted to the few long-term trials of 24 to 52 weeks duration.	**1 RCT** [7]	All A n(%) vs. All E/S n(%); Difference (95%CI) Serious: 9 (1.3) vs. 1 (0.2); -1.1 (-2.3, 0.0) **No Signal** Adverse events: All Rosuvastatin 5,10 +Ezetimib10 vs. All Rosuvastatin 10,20: n (%); Difference (95%CI) Serious: 0 vs. 2 (0.9%); -0.9 (-3.3, 0.8) Serious Drug-related: 10 (4.5%) vs. 6 (2.7%); 1.8 (-1.9, 5.7)		Simvastatin Label Change: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis. Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. 2) On Rosuvastatin calcium Label Change: Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Crestor. These risks can occur at any dose level, but are		
	1 RCT [12]	**No Signal** Fenofebric acid + low dose statin vs. low dose statin Adverse Events- n (%): Serious: 8 (3) vs. 4 (2); 95% CI: NR				

				increased at the highest dose (40 mg).		
Cancer. Evidence pertained to all available trial populations and not only those in need of intensive treatment. Some data were available for individuals at any risk level and statin dose. One 5-year omega-3 trial of 18,645 participants demonstrated no significant difference in the incidence of cancer, with an overall rate of 3 percent. With two 24-48-week statin-ezetimibe trials of 971 participants, the rate of incident cancer was 1 percent, with no significant difference between treatments. Cancer was too rare in a single small statin-niacin trial to permit any conclusion. No evidence was available for statin-fibrate and statin-BAS combinations. While the available data do not suggest an increased incidence of cancer with ezetimibe or omega-3 combinations, the power to detect small differences in the rates of conditions, such as cancer which may have a long latency prior to presentation, is limited given the current data.	**No evidence**	**No Signal**		No alerts	See above	See above
Key Question 2. Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?						
LDL-c Targets, Short-Term Side				8 FDA alerts	1 expert stated that the	Possibly out of

Effects, Tolerability, and Adherence Surrogate markers are biological markers that are linked to the occurrence of disease and used as targets for therapy. The NCEP ATP report sets treatment goals for various risk categories. In this report, we examine the proportion of individuals attaining the LDL-c goals set by the ATP III panel, the effect on LDL-c and HDL-c levels, the total cholesterol:HDL-c ratio, and markers of atherosclerosis. **Participants attaining ATP III LDL-c goals.** The available evidence is of very low quality for all comparisons of combination with monotherapy. For individuals requiring intensive therapy, two trials employing fixed dose or titrations could be statistically combined. <u>Compared with a higher dose statin alone, statin-ezetimibe combination demonstrated a greater probability of reaching treatment goals</u>. A single trial using a statin-fibrate combination demonstrated no significant difference in the number of participants reaching goals compared to a higher dose statin. No evidence comparing higher dose statin	**1 Meta analysis** [8]	**No signal** The finding is in agreement with the original CER, favoring the add-on ezetimibe over statin titration and was statistically significant (OR: 2.45, 95% CI (1.95, 3.08), $p < 0.007$).		**3 FDA Notifications on** Simvastatin: <u>1) Drug Safety Communication</u>: Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug. <u>2) Label Change</u> Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis -Diltiazem: Do not exceed 40 mg simvastatin daily -The combined use of simvastatin in patients receiving diltiazem should not exceed 40 mg daily unless the clinical benefit is likely to outweigh the increased risk of myopathy.	conclusion is not still valid. 2 experts stated that this conclusion is still valid.	date

monotherapy with any of the remaining combinations was available for participants requiring intensive treatment. Substantially more information was available for statin-ezetimibe combination therapy in which the treatment comparison was not necessarily a higher dose of statin. In 88 percent of 18 trials conducted in a population in need of intensive treatment, combination therapy was more likely than statin monotherapy to help participants reach LDL-c targets.				- Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. 3) Label Change Post marketing experience - fatal and non fatal hepatic failure (added)		
Participants attaining ATP III LDL-c goals- Continued: Likewise, 96 percent of 23 trials favored the statin-ezetimibe combination when all trial populations using various statins as the two treatments were included.	**1 Non RCT** [23]	**1 Signal (Other)** The findings from this retrospective study is in conflict with the original CER: ezetimibe/simvastatin vs. rosuvastatin LDL-c goal achievement (2001 and 2004):(58.4% vs. 81.4%; p<0.01 and 46.4% vs. 31.5%; p<0.01)favoring the monotherapy.		**2 FDA Notifications** 1) On Ezetimib/ Simvastatin Label Change: Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis. Cases of myopathy/rhabdomy	See above	See above

				olysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. 2) On Rosuvastatin calcium <u>Label Change:</u> Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Crestor. These risks can occur at any dose level, but are increased at the highest dose (40 mg).		
Participants attaining ATP III LDL-c goals- CONTINUED No evidence was available for the statin-omega-3 combination. Sparse				See above	See above	See above

evidence precluding meaningful conclusions was identified for statin-fibrate (two trials: Table 19: "One trial using a higher dose statin monotherapy in participants with diabetes mellitus showed no significant results. Another study comparing the same statin and same dose in combination therapy and monotherapy favored combination therapy."), statin-niacin (one trial), and statin-BAS (one trial) combinations across various doses and populations.	**1 RCT**[17]	**No Signal** The finding was in agreement with the original CER favoring combination therapy in achieving the LDL cholesterol (<100 mg/dl) goals ($p < 0.01$).				
LDL-c percentage mean change from baseline: When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was **either insufficient or absent** for statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations. Scant evidence from two **statin-ezetimibe** trials was not statistically combined because of heterogeneity, but both trials indicated significant additional reductions of 10 to 20 percent favoring statin-ezetimibe combination therapy over monotherapy.	**1 RCT** [7]	**No Signal** The finding is in agreement with the original CER favoring the combination therapy: Ezetimibe (10 mg)+ rosuvastatin (5mg) vs. rosuvastatin (10mg) LDL percentage change -12.3 ; $p<0.001$ And Ezetimibe (10 mg)+ rosuvastatin (10mg) vs. rosuvastatin (20mg)		See above	See above	See above

		LDL percentage change -17.5; p<0.001				
LDL-c percentage mean change from baseline- Continued: More data were observed for individuals requiring intensive therapy when combinations were compared with any dose of statin. Substantial heterogeneity precluded statistical analysis of 18 statin-ezetimibe and 4 statin-BAS trials. However, all statin-ezetimibe trials favored combination treatment, with mean additional reductions of 4 to 27 percent. Inconsistent results were found for statin-BAS trials, while evidence was insufficient for statin-niacin, statin-BAS, and statin-omega-3 combinations.	**1 RCT** [9] **1 RCT**[18]	**No Signal** The finding was in agreement with the original CER favoring the combination therapy: Ezemitib +Atorvastatin vs. Atorvastatin+ placebo The mean LDL-c levels at the: Baseline (102±29 vs. 77±10; p<0.001) vs. Final follow up (99±21 vs. 86±14;P<0.001); p=NS; p<0. **No Signal** Ezetimibe + atorvastatin vs. atorvastatin The mean LDL-c levels at the: Baseline (102±29 vs. 99± 21; p=NS) vs. Final follow up (77±10 vs.86±14; p<0.001).		See above	See above	See above

	1 RCT[5]	**No Signal** simvastatin + ezetimibe vs. simvastatin for statin naïve group: LDL-C at Baseline: (118±9 mg/dl) vs. (118±10 mg/dl); p=NR LDL-C at year 1 (67±7 mg/dl) vs. (91±8 mg/dl); p < 0.05 LDL-C at year 2 68±10 mg/dl vs. 83 ±11 mg/dl				
	1 RCT[8]	**No Signal** The findings were in agreement with the original CER favoring the combination therapy. WMD in LDL-C: -14.1% (-16.1, -12.1); p<0.001. Pooled effect estimate (%) (95% CI) in LDL-c: -14.1 (-16.1, -12.1); p<0.001; I^2 % : 65.8; Heterogeneity p= 0.001				

	1 RCT [6]	**No Signal** The finding was in agreement with the original CER favoring the combination therapy: Ezetimibe+Statin vs. Statin The LDL-c difference at the baseline versus 6 weeks: -88± 21 vs. -70±20; p<0.005.				
Across all trial populations, when lower doses of statins in combination were compared with higher doses of the same statin monotherapy, significant additional LDL-c reductions of 3 to 20 percent were observed with statin-ezetimibe combinations (six trials); however, heterogeneity precluded a statistical estimate. Evidence was insufficient or absent for each of the remaining combinations.	**1 RCT**[11]	**No Signal** The finding was in agreement with the original CER favoring the combination therapy: Simvastatin+Ezemitib vs. Simvastatin: LDL-C mg/dL (mmol/L)% Change -49 vs. -43; p<0.0001		See above	See above	See above
Across various doses of statins in combination and as monotherapy in all trial populations, significant LDL-c reductions were found with statin-ezetimibe combination (35 trials, of which 94 percent showed 4 to 27 percent additional reduction in LDL-c) and statin-BAS (11 trials, of which 8	**1 RCT** [10]	**No Signal** The finding was in agreement with the original CER favoring the combination therapy: (Ezemitib 10mg+ Simvastatin 20mg vs.		See above	See above	See above

trials employing similar doses showed significant, 8 to16 percent, additional reductions favoring combination). With two statin-omega-3 trials, monotherapy was superior.		Atorvastatin 10mg) Mean difference LDL :-14.7; p<0.001 (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 20mg) Mean difference LDL:-7.5; p<0.001 (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg) Mean difference LDL:-8.2;p<0.001				
	1 RCT [22]	**No Signal** Mean differences: (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 10mg) LDL-C :-13.1; p<0.001 (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 20mg) LDL-C:-10.2; p<0.001 (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg) LDL-C:-8.0; p<0.001				

	1 Non RCT [23]	**1 Signal** The finding was in conflict with the original CER favoring monotherapy over combination therapy: ezetimibe/simvastatin vs. rosuvastatin Least-squares mean % change inLDL-C from baseline: -35 vs. -46.7; p<0.001				
LDL-c continued- percentage mean change from baseline- Indeterminate efficacy was noted for the few statin-fibrate and statin-niacin trials. "One trial in a North America population, 90 percent of European descent, with prior use of statins showed a statistically significant difference in means of -5.4 percent (95% CI -8.39, -2.41) in favor of the statin plus fenofibrate combination." Page 65	**1 RCT** [17]	**No signal** (Statin +fibrate vs. Statin in all trial population): The findings is in agreement with the original CER in favor of combination therapy: The mean percentage change was 11.7% vs. -5.9%, p =0.019.		See above	See above	See above
	1RCT[12]	**1 Signal** The findings showed almost comparable LDL-c levels in both groups: The LDL-c level reduction was (37% vs. 36%) in population				

		receiving Fenofebric acid + low dose statin vs. low dose statin and (39% vs. 43 %) in population receving (Fenofebric acid +moderate dose statin vs. moderate dose statin).				
LDL-c continued- percentage mean change from baseline- page 65 "Results were similar, but not statistically significant, in two trials exclusively in participants requiring intensive lowering therapy because of diabetes mellitus, with a pooled mean difference of 4.82 percent (95% CI -0.35, 9.99)"	**1 RCT** [21]	**1 Signal** Statin +fibrate vs. Statin in population requiring intensive lipid therapy: A statistically not significant finding from the original CER was supplemented with a statistically significant result from this trial favoring the combination therapy. The baseline vs. 12 months LDL-c levels were: (188±17 vs.184±19) vs. (112±14 vs. 142±17);p<0.001.		See above	See above	See above
HDL-c. <u>There is lack of evidence permitting meaningful conclusions from trials comparing a combination with higher dose of statin monotherapy in populations requiring intensive treatment.</u>	**1 RCT**[20]	**1 signal** Statin lower dose +Ezetimibe vs. Statin higher dose in population requiring intensive lipid therapy: HDL-c mean percentage		See above	See above	See above

	1 RCT [7]	change to be: <u>Wk 6</u> 2, 95% CI (0.3, 4); p=0.021 <u>Wk 12</u> 3, 95% CI (2,5);p< 0.001 **1 Signal** Ezetimibe (10 mg)+ rosuvastatin (5mg) vs. rosuvastatin (10mg) <u>HDL percentage change</u> -4.5 ; p=0.017 And Ezetimibe (10 mg)+ rosuvastatin (10mg) vs. rosuvastatin (20mg) <u>HDL percentage change</u> -0.3;p=NR				
HDL-c continued: In trials comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, there was evidence of 1.5 percent increment in HDL-c favoring statin-ezetimibe	**1 RCT** [14]	**1 Signal** Findings in conflict with the original CER not favoring the combination therapy: <u>Baseline vs. 6 weeks (mg/dl)</u> <u>Fenofibrate +Atorvastatin : HDL:</u> 48±13 vs. 48±13;		See above	See above	See above

(15 trials) and statin-fibrate combination therapy, and of no significant difference between monotherapy and statin-BAS combination (four trials).		p=0.006 Vs. Atorvastatin HDL: 45±13 vs. 46±11; p=NR				
	1 RCT[18]	**1 Signal** In conflict with the original CER, the findings did not favor combination therapy: Ezetimibe + atorvastatin vs. atorvastatin HDL(mg/dl) Baseline: 37±8 vs. 37±8; p=NS Final: 38±7 vs. 37±9;p=NS				
	1 RCT[21]	**No Signal** In agreement with the original CER, the findings favored combination therapy: Fenofibrate+ simvastatin vs. simvastatin HDL-C: Baseline (41± 9 vs. 46±9.5);p=NR vs. 12 months (55±11 vs. 51±7.5); p<0.001				

	1 RCT[5]	**1 Signal** The findings did not favor the combination therapy and there was a slight reduction the HDL-c level from baseline to final follow up: simvastatin + ezetimibe vs. simvastatin for statin naïve group: HDL-C (mg/dl) at Baseline: (48±4) vs. (45±4); p=NR HDL-C(mg/dl) at year 1 (42±3) vs. (46±3); p =NR HDL-C (mg/dl) at year 2 (46±3) vs. (44 ±4);p=NR				
HDL-c Continued: Insufficient evidence compared statin-niacin and statin-omega-3 combination with monotherapy in this population.	**1 RCT**[24]	**1 Signal** (Statin +niacin vs. Statin): Insufficient evidence in the original CER is supplemented this clinical trial favoring the combination therapy: Mean HDL –c (mg/dl) change (baseline vs. final follow up in combination arm): 34.8±5.9 vs.		**2 FDA Notifications** (Label Change) for: 1) Niacin extended realease/simvastatin, and 2) Niacin extended release/lovastatin Reproting the adverse events that were not the outcome of interest	See above	See above

		44.1±11.3; p=NR Mean HDL –c (mg/dl) change (baseline vs. final follow up in monotherapy arm): 35.3±5.9 vs. 39.1±7.7 ;p=NR		in this report.		
HDL-c Continued: When trials were not restricted to populations in need of intensive treatment, no significant difference in change in HDL-c was noted for simvastatin in combination with ezetimibe vs. higher doses of simvastatin alone (five trials). Evidence from a single trial favored statin-niacin combination, and showed no difference between statin-fibrate and monotherapy.	**1 RCT**[11]	**No Signal** No difference was observed in combination vs. montherapy: Simvastatin+Ezemitib vs. Simvastatin: HDL-C mg/dL (mmol/L) % Change 0.3 vs. 0.3; p=NR		See above	See above	See above
No consistent effect was noted for the statin-ezetimibe combination across diverse trial populations employing various statins and doses.	**4 RCTs**	The findings from the identified studies (26, 97, 8, 20) were in agreement with the original CER showing inconsistent results for HDL-c levels: **No Signal**		See above	See above	See above

	1 RCT[6]	HDL (mg/dl) difference from baseline: -1.6±4 vs.-1.2±6; p:NR				
	1 RCT [9]	**No Signal** Ezemitib +Atorvastatin vs. Atorvastatin+ placebo HDL(mg/dl) baseline vs. final (37±8 vs. 38±7; p=NS) vs. (37±8 vs. 37.9;p=NS);p=NS; p=NS				
	1 RCT [10]	**No Signal** Treatment differences: (Ezemitib 10mg+ S20mg vs. A 10mg) HDL: 2.4; p=NR (Ezemitib 10mg+ S 20mg vs. A 20mg) HDL:3.3; p<0.05 (Ezemitib10mg+S 40mg vs. A40mg)				

		HDL:2.1;p=NR				
	1 RCT [22]	**No Signal** Treatment differences: (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 10mg) HDL-C: 3.4; p=0.05 (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 20mg) HDL-C:1.2;p=NR (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg) HDL-C:4.0;p<0.01				
HDL-c Continued: However, across various statins and doses in all populations, significant advantages of the statin-omega-3 and statin-fibrate combinations were noted for HDL-c increment when compared with monotherapy (three trials each), while no significant difference was noted for the statin-BAS combination (nine trials). Five of the six statin-niacin trials favored combination, the exception being the one trial that employed high-dose rosuvastatin in	**2 RCTs** **1RCT** [12]	The findings from 2 clinical trial (31,62) were in agreement with the original CER favoring the combination therapy: **No Signal** fenofibrate +statin. Fenofebric acid + low dose statin vs. low dose statin HDL-c level incensement: 20% vs. 8%		See above	See above	See above

both treatments.	**1 RCT** [19]	**No Signal** P-OM3+ Simvastatin vs. Simvastatin +Placebo % Change in HLDL (mg/dl) For LDL< 80.4: 4 (0,22) vs. -1(-7, 5) For LDL< 80.4 - <99.0: 2 (-4,7) vs. -1(-9,6) For LDL >=90 4(-3,13) vs. -1(-5,2)				
Total cholesterol:HDL-c ratio. When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either absent or based on single-trial data, precluding robust conclusions across any combination therapy. A single ezetimibe trial compared lower dose simvastatin in combination vs. higher dose of simvastatin monotherapy in participants requiring intensive lipid-lowering therapy; results favored the combination therapy, demonstrating 14 percent additional reduction.	**2 RCTs** **1 RCT** [20]	In agreement with the findings of the original CER, two clinical trial (71, 14) favored the combination therapy: **No Signal** Ezetimib + statin vs. statin monotherapy: TC/HDL ratio (mg/dl) mean % change Wk 6 -9, 95% CI (-11, -7); p<0.001 Wk 12		See above	See above	See above

	1 RCT [7]	-5, 95% CI (-7, -2); p<0.001 **No Signal** Ezetimibe (10 mg)+ rosuvastatin (5mg) vs. rosuvastatin (10mg) T/HDL ratio percentage change -1.4; p=NR And Ezetimibe (10 mg)+ rosuvastatin (10mg) vs. rosuvastatin (20mg) T/HDL ratio percentage change -10.6; p<0.001				
Total cholesterol:HDL-c ratio- Continued: When comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, additional data were available. Significant additional reductions of 3 to 20 percent favoring statin-ezetimibe combination therapy were noted in all 10 trials, with substantial heterogeneity precluding meta-	**4 RCTs** **1 RCT** [8]	The findings from the identified studies (16, 30, 26, 97) were in agreement with the original CER favoring the combination therapy versus the monotherapy: **No Signal** Ezetimibe+statin vs. statin fixed- and random-effects meta-analyses:		See above	See above	See above

analysis. Evidence was neutral for the statin-fibrate combination (two trials). For other combinations, evidence was either insufficient or absent. Across all available populations, evidence comparing a lower statin dose in combination with a higher dose as monotherapy demonstrated no significant difference between statin-ezetimibe combination and monotherapy. Evidence was insufficient for statin-fibrate combination. Across various statins and doses in all trial populations, 20 statin-ezetimibe trials were not meta-analyzed because of substantial heterogeneity; however, combination treatment was significantly favored in all but one trial. Evidence favored statin-omega combination, did not show a difference for statin-fibrate, was insufficient for statin-niacin, and was totally absent for statin-BAS.	**1 RCT[11]** **1 RCT[10]**	Pooled effect estimate (%) T/ HDL-c: -10.8 (-12.4, -9.2); p<0.01; I^2 %: 18.7; Heterogeneity p= 0.287 **No Signal** imvastatin+Ezemitib vs. Simvastatin: TC/HDL-C mg/dL % Change from baseline -35 vs. -31; p<0.0001 **No Signal** Treatement differences: (Ezemitib 10mg+ Simvastatin 20mg - Atorvastatin 10mg) TC/HDL: -10.8; P<0.001 (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 20mg)				

	1 RCT [22]	TC/HDL: -6.2; P<0.001 (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg) TC/HDL: -6.9;P<0.001 **No Signal** Treatement differences: (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 10mg) T/HDL-C: -8.8; p<0.001 (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 20mg) T/HDL-C: -5.3; p<0.001 (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg) T/HDL-C: -5.9; p<0.001				
Measures of atherosclerosis. Carotid intimal media thickness (IMT) can be measured by ultrasound and correlates	**1 RCT**[5]	**1 Signal** In 67 patients atherosclerosis measured by		See above	See above	See above

with the presence of atherosclerotic plaque and vascular risk factors. Previous research has shown that statin treatment reduces the progression of this marker. Two trials were available that compared mean change from baseline in the IMT with combination therapy compared to statin monotherapy. One trial of 642 evaluable participants requiring intensive lipid lowering compared simvastatin plus ezetimibe with identical-dose simvastatin monotherapy and yielded indeterminate results. Another trial of 149 evaluable participants requiring intensive lipid-lowering therapy and using mixed statins with niacin and as monotherapy also demonstrated indeterminate results.		magnetic resonance imaging (MRI) in the superficial femoral artery(SFA) in peripheral arterial disease (PAD). Statin-naïve patients (n = 34) were randomized to simvastatin 40 mg (S, n = 16) or simvastatin 40 mg + ezetimibe 10 mg (S + E, n = 18). Patients already on statins but with LDL-C >80 mg/dl had open-label ezetimibe 10 mg added (E, n = 33).Statin initiation with or without ezetimibe in statin-naïve patients halts progression of peripheral atherosclerosis. When ezetimibe is added to patients previously on statins, peripheral atherosclerosis progressed. Thus, ezetimibe's effect on peripheral atherosclerosis may depend upon relative timing of statin therapy.				
Adherence and harm. For the comparison of a specific statin in combination with a higher dose of its monotherapy across all trial populations, insufficient evidence was available for all combinations except	**2 RCTs**	In agreement with the original CER, the findings from 2 clinical trial (14, 71) showed no significant difference between the groups.		See above	See above	See above

statin-ezetimibe, which showed no significant differences between treatments for the outcomes of withdrawal due to adverse events and liver toxicity (defined as **AST/ALT** above three times the upper limit of normal). Most trials had a short duration of treatment and follow up. Conclusions summarized below pertain to the comparisons of various statins and doses in combination with various statin monotherapies in all trial populations.	**1 RCT** [7]	**No Signal** Adverse events: All Rosuvastatin 5,10 +Ezetimibe 10 vs. All Rosuvastatin 10,20: n (%); Difference (95%CI) Discontinuations Drug-related: 5 (2.3) vs. 0; 95% CI:NR Drug-related: 10 (4.5%) vs. 6 (2.7%); 1.8 (-1.9, 5.7) AST & ALT ≥ 3upper limit of normal 1/219 (0.5) vs. 0/214; 0.5 (-1.3, 2.5); p= 0.327				
	1 RCT [20]	**No Signal** Adverse Event n(%) A10+ E10 vs. A20/40 Discontinuations Drug related; 6 (1%) vs. 3 (1%) Discontinuations Drug related Serious: 4 (1%) vs. 3 (1%)				

		AST≥ 3 x ULN: 1/520 (<1%) vs. 3/520 (1%); p>0.05 ALT≥ 3 x ULN: 2/520 (<1%) vs. 5/520 (1%); p>0.05				
For Fenofebric acid +statin vs. statin please refer to the page 63 of the original CER full report.	**2 RCTs** **1 RCT** [12]	The finding form 2 clinical trial (31, 56) was in agreement with the original CER. **No Signal** Fenofebric acid + low dose statin vs. low dose statin ALT incidence≥3 x ULN: 5 (2%) vs.0; p=NR AST incidence≥ x ULN: 2 (1%) vs. 0; p=NR CPK≥ 10 x ULN 0 vs. 0; p=NR Adverse Events- n (%): Leading to discontinuation:		See above	See above	See above

	1 RCT [17]	36 (14) vs. 11 (5) Any treatment related: 75 (29) vs. 43 (18) Myalgia: 8 (3) vs. 4 (2) **No Signal** Fenofibrate +Pravastatin vs. Parvastatin <u>Incidence of adverse events- n(%):</u> Drug-related adverse event: 13 (10.6) vs. 12 (9.6) Serious drug-related adverse event: 1 (0.8) vs. 0 Discontinued due to adverse event: 5 (4.1) vs. 5 (4.0)				
Adherence and harm- Continued: <u>Early withdrawal due to adverse events was</u> more likely for the combination of statin plus niacin than	**1 RCT[24]**	**No Signal** The finding was in agreement with the original CER. Placebo+ Statin vs.		See above	See above	See above

for statin therapy alone (10 trials with an average duration of 24 weeks). No significant difference was noted for other combinations.		Extended-release niacin+ statin Discontinuation of study drug after randomization- no (%): 341 (20.1) vs. 436 (25.4); p<0.001				
Adherence and harm- Continued: Ezetimibe plus statin vs. statin in all trial population and various doses: Please refer to table 7 on page 37 of the original CER.	**1 RCT [22]**	**No Signal** The findings from was in agreement with the original CER results demonstrating no significant differences between groups. Adverse events: All Atorvastatin n(%) vs. All Ezetimibe / Simvastatin n(%); Difference (95%CI) Drug-related: 26 (3.8) vs. 15 (3.3); -0.5 (-2.7, 1.9) Serious drug-related: 1 (0.1) vs.0; -0.1 (-0.8, 0.7) Discontinuation Drug-related: 7 (1.0) vs. 4 (0.9); -0.1 (-1.4, 1.3) Discontinuation serious		See above	See above	See above

		Drug-related: 1 (0.1) vs. 0; -0.1 (-0.8, 0.7)				
Adherence and harm- Continued: Compared with statin monotherapy, more participants developed at least one adverse event with statin-BAS combination (four trials). Inconsistent results were obtained when statin-niacin combination was compared with statin monotherapy. However, three of six trials showed significantly more participants experiencing adverse events with combination than with monotherapy.	**No Evidence**	**No Signal**		See above	See above	See above
Adherence and harm- Continued: Available evidence did not indicate significant differences between participants developing **AST/ALT** above 3 times the upper limit of normal and/or **hepatitis, CPK** above 10 times the upper limit of normal, or **myalgia** for a comparison of any combination with statin monotherapy.	**3 RCTs** **1 RCT** [17]	The finding form 2 clinical trial (56, 55) were in agreement but the finding from trial (97) was in conflict with the original CER for AST>3xULN. **No Signal** Fenofibrate +Pravastatin vs. Parvastatin Incidence of AST and ALT ≥3 times upper limit of			See above	See above

		normal: 0 vs. 0; p=NR		**1 FDA Notification** <u>Drug Safety Communication</u>: Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug.		
	1 RCT [15]	**No Signal** Fenofibrate +statin vs. statin Serious Adverse Events n (%): severe muscle aches/pains not associated with known activities; n(%): 1110 (40.1) vs. 1115 (40.5);p= 0.79 ALT ever ≥ 3X ULN n(%); 52 (1.9) vs. 40 (1.5);p= 0.21 CPK ever ≥ 10X ULN ; n(%): 10 (0.4) vs. 9 (0.3); p= 0.83				
	1 RCT [22]	**1 Signal** All A n(%) vs. All E/S n(%); Difference (95%CI) ALT ≥ 3ULN 2 (0.3%) vs. 1 (0.2%); -0.1 (-0.9, 1.0); p=0.81 AST≥3ULN				

		1 (0.2%) vs. 5 (1.1%); 1.0 (0.1, 2.5); p=0.03 CPK≥ 10ULN 0 vs. 1 (0.2%); 0.2 (-0.4,1.3); p=0.22				
Adherence and harm- Continued: <u>In addition, no participant developed rhabdomyolysis in</u> any of the 27 RCTs investigating the five statin combination therapies, 85 percent of which were short term. No significant difference in treatment adherence was noted for statin-ezetimibe and statin-niacin combinations compared to monotherapy. The statin-BAS trials could not be meta-analyzed due to inconsistent and unexplained direction and magnitude of effects on adherence across five trials.	**2 RCTs** **1 Non RCT** [13] **1 RCT** [15]	The findings from two clinical trials were in conflict with the original CER demonstrating patients developing rhabdomyolysis **1 Signal:** Statins and fenofibrate vs. statin: Adjusted IRR (95% CI): 3.75 (1.23–11.40) **1 Signal** Fenofibrate +statin vs. statin Rhabdomyolysis ; n (%): 4 (0.1) vs. 3 (0.1); p= 1.00		**2 FDA Notification** **Both on Label Change:** **1)** For Rosuvastatin: Skeletal Muscle Effects: Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Crestor. These risks can occur at any dose level, but are increased at the highest dose (40 mg). **<u>2)</u>** For Simvastatin: <u>WARNINGS and</u>	See above	See above

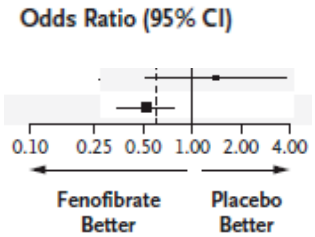
				PRECAUTIONS Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis -Diltiazem: Do not exceed 40 mg simvastatin daily -The combined use of simvastatin in patients receiving diltiazem should not exceed 40 mg daily unless the clinical benefit is likely to outweigh the increased risk of myopathy. - Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products.		
Key Question 3. Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?						
Evidence in subgroups. ***Participants with diabetes mellitus.***	**No Evidence**	**No Signal**		3 FDA alerts	1 expert stated that the	Possibly out of date

Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy for any relevant outcomes.					conclusion is not still valid. 2 experts stated that this conclusion is still valid; one expert have commented that conclusion from ACCROD (54) should be noted.	
Participants with diabetes mellitus-Continued: Across various statin doses in combination and monotherapy, no evidence was available for statin-niacin, statin-BAS, and statin-omega-3 combinations.	**No Evidence**	**No Signal**				
Participants with diabetes mellitus-Continued: <u>Compared with statin monotherapy, the statin-ezetimibe combination allowed more participants with diabetes to reach ATP III LDL-c goals when monotherapy was of similar statin dose and potency to combination statin (very low quality</u>	**1 RCT[6]**	**No Signal** Finding in agreement with the original CER. Ezetimibe+Statin vs. Statin <u>LDL (mg/dl) difference from baseline:</u> -88± 21 vs. -70±20; p<0.005		See above	See above	See above

of evidence) and allowed greater additional reductions in LDL-c, ranging from 4 to 26 percent; TC:HDL-c ratio, 3 to 17 percent; and non-HDL-c, 4 to 24 percent. There was inconsistent evidence for a change in HDL-c between combination and monotherapy treatments.		HDL (mg/dl) difference from baseline: -1.6±4 vs.-1.2±6; p:NR				
Participants with diabetes mellitus-Continued: Meta-analysis of two statin-fibrate trials demonstrated no significant difference between treatments for LDL-c reduction, but a significant increase in HDL-c of 5 percent favored the combination. There was insufficient evidence on statin-fibrate combination for other outcomes in participants with diabetes mellitus, including one trial that examined mean percentage reduction in triglyceride in 164 participants, with additional mean reduction of 14 percent favoring combination therapy.	**1RCT** [15] **1 RCT** [16]	**No Signal:** Findings from ACCROD trial (n=5518 diabetic patients; 4.7 yrs follow up) Fenofibrate +statin vs. statin Mean LDL-C (mg/dl) (baseline vs. baseline) vs. (end of follow vs. end of follow up): (100.0 vs. 101.1; p=0.16) vs. (81.1vs. 80.0; p=0.16) Mean HDL –c (mg/dl) (baseline vs. baseline) vs. (end of follow vs. end of follow up): (38.0 vs. 38.2; p=0.27) vs. (41.2vs. 40.5; p=0.01) **1 Signal** Fenofibrate+Simvastatin vs. Simvastatin+placebo Median HDL(mg/dl) (Baseline vs. 1year: 38 vs. 40) vs. (38 vs.39); p=0.002		**1 FDA Notification** (Safety communication) on fenofibric acid (Trilipix, Abbott), stating that the drug may not lower the risk of major cardiovascular events based on the ACCORD lipid trial.	See above	See above

		Median LDL (mg/dl) (Baseline vs. 4 year: 93 vs. 78) vs. (Baseline vs. 4 year: 93 vs. 78);p=0.68				
Participants with diabetes mellitus-Continued: Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial,	**1RCT[15]**	**1 signal** Findings from ACCROD lipid trial (n=5518 diabetic patients; 4.7 yrs follow up) showed 221 events in the combination therapy and 203 events in monotherapy groups with HR: 0.91 and 95% CI (0.75, 1.10); p=0.33.		See above	See above	See above
Participants with diabetes mellitus-Continued: and evidence for vascular death was absent across all combinations using various statin doses.	**1 RCT [15]**	**1 signal** Findings from ACCROD lipid trial (n=5518 diabetic patients; 4.7 yrs follow up) showed 221 events in combination therapy and 203 events in monotherapy groups with HR: 0.91 and 95% CI (0.75, 1.10); p=0.33. **1 signal** The same study showed 186 events in the intervention group (n=2753) and 173		**1 FDA Notifications** On Simvastatin: Label Change Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis -Diltiazem: Do not exceed 40 mg simvastatin daily -The combined use of simvastatin in patients receiving diltiazem should not	. One expert said "No" but has added the following	See above

	1 RCT [16]	events in the control group (n=2765) due to Non fatal MI. HR: 0.91, 95% CI (0.74, 1.12); p=0.39. **1 signal** The same study demonstrated that there were 48 events in the combination therapy group (n=2753) and 51 events in the monotherapy group (n=2765) due to any stroke. HR: 1.05, 95% CI (0.71, 1.56); p=0.80. Fenofibrate+Simvastatin vs. Simvastatin+placebo <u>Sub group analysis:</u> Patients with Triglyceride level>= 204 mg/dl & HDL-c <=34mg/dl; [no. with progression of retinopathy/ total no. (%)] : Yes 10/119 (8.4) 7/116 (6.0) No 41/684 (6.0) 73/669 (10.9)		exceed 40 mg daily unless the clinical benefit is likely to outweigh the increased risk of myopathy. - Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products.	comment: "No. But the reduced risk and progression of retinopathy and albuminuria (ie. microvascular disease) in patients with type 2 diabetes mellitus in the ACCORD-EYE study is important to note." This pointed in this report under Ref ID: 54). He also refers the readers to the results of the ACCORD (55) that is included in this report.	

		 P= 0.11 (for interaction)				
Participants with established vascular disease. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes in individuals with pre-existing vascular disease. Across various statin doses in combination and monotherapy, there was insufficient evidence examining the statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations with respect to statin monotherapy. Compared with statin monotherapy, statin-ezetimibe combination therapy allowed more participants to reach ATP III LDL-c goals and to reach 9 to 27 percent additional reduction in LDL-c. No significant difference was noted for change in HDL-c for this combination, and evidence was insufficient for	**1 RCT**[5]	**3 Singals** simvastatin + ezetimibe vs. simvastatin for statin naïve group: LDL-C at Baseline:(118±9 mg/dl) vs. (118±10 mg/dl); p=NR LDL-C at year 1: (67±7 mg/dl) vs. (91±8 mg/dl); p < 0.05 LDL-C at year 2: 68±10 mg/dl vs. 83 ±11 mg/dl HDL-C at Baseline:(48±4 mg/dl) vs. (45±4 mg/dl); p=NR HDL-C at year 1:(42±3 mg/dl) vs. (46±3 mg/dl); p =NR HDL-C at year 2:(46±3		**1 FDA Notification** Ezetimibe/simvastatin (Label Change) Myopathy/Rhabdomyolysis: Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with Vytorin coadministered with lipid-modifying	See above	See above

TC:HDL-c ratio. Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and not estimable for vascular death from one short-term statin-niacin trial registering no event.		mg/dl) vs. (44 ±4 mg/dl);p=NR Plaque volume: baseline vs. year2: 11.5 ±1.4 cm3 - 10.5±1.3 cm3 ; p= NS 11.0 ±1.5 cm3 –10.5±1.4 cm3 ; p= NS In statin + ezetimibe: LDL-C at baseline vs. year 1 vs. year 2 100±4 vs. 80± 6* 77 vs. 77±5; p<= 0.05 Plaque volume: baseline vs. year2 10.0 ± 0.8 vs. 10.8 ± 0.9; p < 0.01		doses of niacin containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive Vytorin 10/80 mg coadministered with lipid-modifying doses of niacin-containing products.		
Participants with baseline LDL-c of 190 mg/dL or above. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes. Across various statin doses in	**No evidence**	**No Signal**		See above	See above	See above

combination and monotherapy, no evidence examined the statin-fibrate, statin-niacin, and statin-omega-3 combinations. Compared with statin monotherapy, the statin-ezetimibe combination allowed 17 percent additional reductions in LDL-c. Insufficient evidence for this combination was available for other outcomes. No significant difference was noted for change in HDL-c with statin-BAS combination, and evidence was inconsistent for a reduction in LDL-c. Insufficient evidence for this combination was available for other outcomes.						
Participants with cerebrovascular disease, females, participants of 80 years of age or older, participants of African descent, participants of Asian descent, and Hispanics. No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females (No available evidence: table 20th of CER). However, one large 5-year trial investigating various	**1 RCT** [12]	**8 signals** In all women study: Fenofebric acid + low dose statin vs. low dose statin HDL-c level incensement: 20% vs. 8% ;p=NR LDL-c level reduction: 37% vs. 36%;P=NR		**1 FDA Notification** Ezetimibe/simvastatin (Label Change) Myopathy/Rhabdomyolysis: Cases of myopathy/rhabdomyolysis have been observed with simvastatin	See above	See above

statins in both treatments among 18,645 Asians resulted in low-quality evidence that there was no significant difference between statin-omega-3 combination and statin monotherapy for the outcome of all-cause mortality.		Adverse Events- n (%): Serious: 8 (3) vs. 4 (2) Leading to discontinuation: 36 (14) vs. 11 (5) Any treatment related: 75 (29) vs. 43 (18) Myalgia: 8 (3) vs. 4 (2) ALT incidence>= 3 upper the limit of normal: 5 (2%) vs.0; p=NR AST incidence>= 3 upper the limit of normal: 2 (1%) vs. 0; p=NR CPK>= 10 x ULN 0 vs. 0; p=NR Fenofebric acid +moderate dose statin vs. moderate dose statin LDL-c level reduction: 39% vs. 43%;p=NR ALT incidence>= upper the		coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with Vytorin coadministered with lipid-modifying doses of niacin containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive Vytorin 10/80 mg coadministered with lipid-modifying doses of niacin-containing products. **1 FDA Notification** (Safety communication) on fenofibric acid (Trilipix, Abbott), stating that the drug may not lower the risk of major		

		limit of normal: 5 (2%) vs. 0 AST incidence>= upper the limit of normal: 2 (1%) vs. 0		cardiovascular events based on the ACCORD lipid trial.		
Participants with cerebrovascular disease, participants of 80 years of age or older, participants of African descent, participants of Asian descent, and Hispanics.- Continued: No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females (No available evidence: table 20th of CER). However, one large 5-year trial investigating various statins in both treatments among 18,645 Asians resulted in low-quality evidence that there was no significant difference between statin-omega-3 combination and statin monotherapy for the outcome of all-cause mortality.	**No evidence**	**4 No Signal**		See above	See above	See above

Abbreviations: CER=comparative effectiveness review; FDA=food and drug administration; WMD: weighted mean difference; PAD: peripheral arterial disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; OR: Odd Ratio; CI: Confidence Interval; CHD: Coronary Heart Disease ;WK: Week; HR: Hazard Ratio; CAD: Coronary Artery Disease; NS: Not significant; NR: Not Reported ACS: Acute Coronary Syndrome; MI: myocardial infarction;S: Statin; x ULN: times upper limit of normal; AST: elevated serum aspartate transaminase; ALT: alanine transaminase;CPK: creatinine phosphokinase

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Appendix A: Search Methodology

All MEDLINE searches were limited to the following journals:

General biomedical – Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine

Specialty journals – American Journal of Cardiology, Circulation, Atherosclerosis, Clinical Chemistry, and Current Medical Research & Opinion

Database: Ovid MEDLINE(R)

Time period covered: 2008 to October 27, 2011
Main Search
Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to October 27 2011>, Embase<1980 to 2011 Week 42>

1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. Heptanoic Acids/
3. (Statin$ or reductase inhibitor$).tw.
4. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
5. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
6. or/1-5
7. exp fatty acids, omega-3/
8. fatty acids, essential/
9. Dietary Fats, Unsaturated/
10. linolenic acids/
11. exp fish oils/
12. (n 3 fatty acid$ or omega 3).tw.
13. eicosapenta?noic.tw,hw,rw.
14. docosahexa?noic.tw,hw,rw.
15. alpha linolenic.tw,hw,rw.
16. (linolenate or cervonic or timnodonic).tw,hw,rw.
17. (mediterranean adj diet$).tw.
18. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
19. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
20. (fish adj2 oil$).tw.
21. (cod liver oil$ or marine oil$ or marine fat$).tw.
22. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
23. (fish consumption or fish intake or (fish adj2 diet$)).tw.
24. or/7-23

25. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
26. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
27. Cholestyramine Resin/
28. Colestipol/
29. (colestimide or colestilan or colestipol).tw.
30. or/25-29
31. ezetimibe.mp.
32. 163222-33-1.rn.
33. (cholester$ adj3 inhibit$).tw.
34. or/31-33
35. (fibrate$ or fibric acid$).tw.
36. Clofibric acid/
37. Clofibrate/
38. Bezafibrate/
39. Gemfibrozil/
40. Fenofibrate/
41. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
42. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
43. or/35-42
44. niacin/
45. nicotinic acids/
46. niacin.tw.
47. or/44-46
48. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
49. Drug Therapy, Combination/
50. (combination adj3 therapy).tw.
51. add-on therapy.tw.
52. or/49-51
53. 6 and (or/24,30,34,43,47-48,52)
54. clinical trial.pt.
55. clinical trials/
56. (randomized or randomly or placebo).ab.
57. trial.ti.
58. randomized controlled trial.pt.
59. or/54-58
60. 53 and 59
61. or/24,30,34,43,47-48,52
62. exp Cardiovascular Diseases/
63. 61 and 62
64. or/6,63
65. limit 64 to systematic reviews
66. limit 64 to meta analysis
67. or/60,65-66
68. limit 67 to english
69. limit 68 to yr="2008 -Current"

70. lancet.jn.
71. jama.jn.
72. "annals of internal medicine".jn.
73. bmj.jn.
74. "new england journal of medicine".jn.
75. american journal of cardiology.jn.
76. circulation.jn.
77. (atherosclerosis or atherosclerosis supplements).jn.
78. clinical chemistry.jn.
79. current medical research & opinion.jn.
80. or/70-79
81. 69 and 80
82. 81 use prmz
83. exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
84. heptanoic acid derivative/
85. (Statin$ or reductase inhibitor$).tw.
86. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
87. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
88. or/83-87
89. Omega 3 Fatty Acid/
90. exp Essential Fatty Acid/
91. exp Unsaturated Fatty Acid/
92. linolenic acid/
93. Fish oils/
94. (n 3 fatty acid$ or omega 3).tw.
95. eicosapenta?noic.tw,hw.
96. docosahexa?noic.tw,hw.
97. alpha linolenic.tw,hw.
98. (linolenate or cervonic or timnodonic).tw,hw.
99. (mediterranean adj diet$).tw.
100. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
101. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
102. (fish adj2 oil$).tw.
103. (cod liver oil$ or marine oil$ or marine fat$).tw.
104. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
105. (fish consumption or fish intake or (fish adj2 diet$)).tw.
106. or/89-105
107. Bile Acid Sequestrant/
108. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
109. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
110. Colestyramine/
111. Colestipol/
112. Colestyramine/

113. Colestilan/
114. (colestimide or colestilan or colestipol).tw.
115. or/107-114
116. Ezetimibe/
117. ezetimibe.mp.
118. 163222-33-1.rn.
119. or/116-118
120. Fibric Acid Derivative/
121. (fibrate$ or fibric acid$).tw.
122. Clofibric acid/
123. Clofibrate/
124. Bezafibrate/
125. Gemfibrozil/
126. Fenofibrate/
127. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
128. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
129. or/120-128
130. nicotinic acid/
131. niacin.tw.
132. or/130-131
133. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
134. Drug Therapy, Combination/
135. (combination adj3 therapy).tw.
136. add-on therapy.tw.
137. or/134-136
138. 88 and (or/106,115,119,129,132-133,137)
139. limit 138 to "treatment (2 or more terms high specificity)"
140. clinical trials/
141. (randomized or randomly or placebo).ab.
142. trial.ti.
143. or/139-142
144. 138 and 143
145. or/106,115,119,129,132-133,137
146. exp Cardiovascular Disease/
147. 145 and 146
148. 88 or 147
149. limit 148 to "reviews (2 or more terms high specificity)"
150. or/144,149
151. limit 150 to english language
152. limit 151 to yr="2008 -Current"
153. lancet.jn.
154. ("jama journal of the american medical association" or "jama the journal of the american medical association").jn.
155. "annals of internal medicine".jn.
156. (bmj or bmj clinical research ed).jn.
157. "new england journal of medicine".jn.

158. "american journal of cardiology".jn.
159. circulation.jn.
160. (atherosclerosis or atherosclerosis supplements).jn.
161. clinical chemistry.jn.
162. ("current medical research and opinion" or "current medical research and opinion supplement").jn.
163. or/153-162
164. 152 and 163
165. 164 use emez
166. 82 or 165
167. remove duplicates from 166
168. 167 use prmz
169. 167 use emez

HARMS
Time period covered: 2008 to October 27, 2011

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to October 27 2011>, Embase<1980 to 2011 Week 42>

1. exp Neoplasms/
2. Rhabdomyolysis/
3. Myocardial Infarction/
4. exp Liver Failure/
5. Stroke/
6. mo.fs.
7. or/1-6
8. (ae or po or to or mo or ci or de or et or co or sc).fs.
9. exp Survival Analysis/
10. exp Death/
11. Risk factors/
12. exp Drug Interactions/
13. Critical Illness/
14. exp Mortality/
15. Abnormalities, drug-induced/
16. exp Drug Hypersensitivity/
17. exp Drug Toxicity/
18. exp Product Surveillance, Postmarketing/
19. Cohort Studies/
20. harm$.mp.
21. ((adverse or serious or severe) adj2 (event$ or reaction$)).mp.
22. ((side or unwanted or adverse or undesire$) adj effect$).tw.
23. (ADR or ADRS or SAE).tw.
24. safety.mp.
25. (bleed$ or haemorrhag$ or hemorrhag$).tw.
26. (toxic$ or gastrotoxic$).tw.

27. (tolerability or tolerance or tolerate$).tw.
28. (relative risk or risks).mp.
29. risk.ti.
30. (cohort adj2 stud$).ti,ab.
31. (treatment emergent or complications).tw.
32. or/8-31
33. Databases as Topic/ or Databases, factual/ or National Practitioner Data Bank/
34. Drug Prescriptions/sn [Statistics & Numerical Data]
35. Hospitalization/sn [Statistics & Numerical Data]
36. Managed Care Programs/sn [Statistics & Numerical Data]
37. (administrative adj2 data$).tw.
38. (PHSHG or Public Health Strategic Healthcare Group or Palo Alto Medical Foundation or PAMF or MedPar or MCBS or Medicare Current Beneficiary Survey or Health Insurance Skeleton Eligibility Write-Off or HISKEW or UPIN or Unique Physician Identification Numbers or CAHPS or HOS or Health Outcomes Study or DSH or Providence BC or Partners Health Care or MEPS or Medical Expenditure Panel Survey or USP MEDMARX or Intensive Care Unit Safety Reporting System or ICU-SRS or i3Magnifi or Ingenix or American Heart Association or PCN or Primary Care Network or CORRONA or VA National Patient database or VA National Patient DB or VANPDB or VA Medicare Database or VAMD or Walgreen$ or Marketscan or Illinois Medicaid or Commercial Food Workers Union or CMS or VHA or Baltimore Veterans Healthcare or Thomson Medstat or Omnicare or HMO Research Network or HMORN or Healthinsight or Utah Population Database or NAMCS or National Ambulatory Medical Care Survey or Pharmetrics or NDTI or Mediplus or Tennessee Medicaid or TENNCARE or GPRD or General Practice Research Database or IMS Disease Analyzer).tw.
39. (California Medicaid or IMS HEALTH National Disease or (Consortium adj Rheumatology Researchers) or Illinois Department or British Columbia).tw.
40. ((French System adj2 Pharmacovigilance) or (ADR Centre adj2 Vietnam) or (WHO Collaborating Programme adj International Drug Monitoring) or (Medicines Evaluation adj Monitoring) or Medicines Evaluation or (Medicaid Pharmaceutical Analysis adj Surveillance)).tw.
41. (VSR or ADRAC or ADR Advisory Committee or CADRMP or Canadian ADR Monitoring Programme or Adverse Reactions Monitoring or BfArM or Voluntary Reporting System or National Reporting System or Farmacovigilanza or Farmacovigilancia or National Drug Monitoring System or National Adverse Reaction Monitoring Programme or Netherlands Pharmacovigilance Foundation or LAREB or National Toxicology Group or Centre for Adverse Reaction Monitoring or Norwegian Medicines Control Authority or Pharmacovigilance or Drug Monitoring Department or Swiss Drug Monitoring Centre or SANZ or Yellow Card or Spontaneous Reporting System or MedMARx or PEM or IMMP or J-PEM or Saskatchewan Administrative Healthcare Utilization Databases or MEMO or BCDSP or Boston Collaborative Drug Surveillance or COMPASS or Uppsala Monitoring).tw.
42. (Saskhealth or Quebec medical claims database or Regie de l'assurance-maladie du Quebec or RAMQ or Nova Scotia Pharmacare or (Health Insurance Commission adj Australia) or Intercontinental Marketing Services Health or medwatch or Linked Health Database or BCLHD).tw.
43. (VAERS or Vaccine Adverse Event Reporting System or adverse events reporting system or AERS or Fallon Health Plan or Harvard Pilgrim or Kaiser Permanente or ACOVE or (Assessing Care adj Vulnerable Elders)).tw.

44. (euromedstat group or euro med stat group).au.
45. or/33-44
46. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
47. Heptanoic Acids/
48. (Statin$ or reductase inhibitor$).tw.
49. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
50. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
51. or/46-50
52. exp fatty acids, omega-3/
53. fatty acids, essential/
54. Dietary Fats, Unsaturated/
55. linolenic acids/
56. exp fish oils/
57. (n 3 fatty acid$ or omega 3).tw.
58. eicosapenta?noic.tw,hw,rw.
59. docosahexa?noic.tw,hw,rw.
60. alpha linolenic.tw,hw,rw.
61. (linolenate or cervonic or timnodonic).tw,hw,rw.
62. (mediterranean adj diet$).tw.
63. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
64. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
65. (fish adj2 oil$).tw.
66. (cod liver oil$ or marine oil$ or marine fat$).tw.
67. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
68. (fish consumption or fish intake or (fish adj2 diet$)).tw.
69. or/52-68
70. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
71. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
72. Cholestyramine Resin/
73. Colestipol/
74. (colestimide or colestilan or colestipol).tw.
75. or/70-74
76. ezetimibe.mp.
77. 163222-33-1.rn.
78. (cholester$ adj3 inhibit$).tw.
79. or/76-78
80. (fibrate$ or fibric acid$).tw.
81. Clofibric acid/
82. Clofibrate/
83. Bezafibrate/
84. Gemfibrozil/
85. Fenofibrate/

86. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
87. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
88. or/80-87
89. niacin/
90. nicotinic acids/
91. niacin.tw.
92. or/89-91
93. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
94. Drug Therapy, Combination/
95. (combination adj3 therapy).tw.
96. add-on therapy.tw.
97. or/94-96
98. 51 and (or/69,75,79,88,92-93,97)
99. or/7,32,45
100. 98 and 99
101. limit 100 to review
102. 100 not 101
103. limit 102 to (english and human and yr=2008-2011)
104. lancet.jn.
105. jama.jn.
106. "annals of internal medicine".jn.
107. bmj.jn.
108. "new england journal of medicine".jn.
109. american journal of cardiology.jn.
110. circulation.jn.
111. (atherosclerosis or atherosclerosis supplements).jn.
112. clinical chemistry.jn.
113. current medical research & opinion.jn.
114. or/104-113
115. 103 and 114
116. 115 use prmz
117. exp neoplasm/
118. rhabdomyolysis/
119. heart infarction/
120. exp liver failure/
121. stroke/
122. or/117-121
123. (ae or to or et or co or si).fs.
124. exp survival/
125. exp death/
126. risk factor/
127. exp drug interaction/
128. critical illness/
129. exp mortality/
130. congenital malformation/
131. exp drug hypersensitivity/

132. exp drug toxicity/
133. exp postmarketing surveillance/
134. cohort analysis/
135. harm$.mp.
136. ((adverse or serious or severe) adj2 (event$ or reaction$)).mp.
137. ((side or unwanted or adverse or undesire$) adj effect$).tw.
138. (ADR or ADRS or SAE).tw.
139. safety.mp.
140. (bleed$ or haemorrhag$ or hemorrhag$).tw.
141. (toxic$ or gastrotoxic$).tw.
142. (tolerability or tolerance or tolerate$).tw.
143. (relative risk or risks).mp.
144. risk.ti.
145. (cohort adj2 stud$).ti,ab.
146. (treatment emergent or complications).tw.
147. or/123-146
148. data base/ or factual database/
149. National Practitioner Data Bank/
150. prescription drug/
151. hospitalization/
152. (administrative adj2 data$).tw.
153. (PHSHG or Public Health Strategic Healthcare Group or Palo Alto Medical Foundation or PAMF or MedPar or MCBS or Medicare Current Beneficiary Survey or Health Insurance Skeleton Eligibility Write-Off or HISKEW or UPIN or Unique Physician Identification Numbers or CAHPS or HOS or Health Outcomes Study or DSH or Providence BC or Partners Health Care or MEPS or Medical Expenditure Panel Survey or USP MEDMARX or Intensive Care Unit Safety Reporting System or ICU-SRS or i3Magnifi or Ingenix or American Heart Association or PCN or Primary Care Network or CORRONA or VA National Patient database or VA National Patient DB or VANPDB or VA Medicare Database or VAMD or Walgreen$ or Marketscan or Illinois Medicaid or Commercial Food Workers Union or CMS or VHA or Baltimore Veterans Healthcare or Thomson Medstat or Omnicare or HMO Research Network or HMORN or Healthinsight or Utah Population Database or NAMCS or National Ambulatory Medical Care Survey or Pharmetrics or NDTI or Mediplus or Tennessee Medicaid or TENNCARE or GPRD or General Practice Research Database or IMS Disease Analyzer).tw.
154. (California Medicaid or IMS HEALTH National Disease or (Consortium adj Rheumatology Researchers) or Illinois Department or British Columbia).tw.
155. ((French System adj2 Pharmacovigilance) or (ADR Centre adj2 Vietnam) or (WHO Collaborating Programme adj International Drug Monitoring) or (Medicines Evaluation adj Monitoring) or Medicines Evaluation or (Medicaid Pharmaceutical Analysis adj Surveillance)).tw.
156. (VSR or ADRAC or ADR Advisory Committee or CADRMP or Canadian ADR Monitoring Programme or Adverse Reactions Monitoring or BfArM or Voluntary Reporting System or National Reporting System or Farmacovigilanza or Farmacovigilancia or National Drug Monitoring System or National Adverse Reaction Monitoring Programme or Netherlands Pharmacovigilance Foundation or LAREB or National Toxicology Group or Centre for Adverse Reaction Monitoring or Norwegian Medicines Control Authority or Pharmacovigilance or Drug Monitoring Department or Swiss Drug Monitoring Centre or SANZ or Yellow Card or

Spontaneous Reporting System or MedMARx or PEM or IMMP or J-PEM or Saskatchewan Administrative Healthcare Utilization Databases or MEMO or BCDSP or Boston Collaborative Drug Surveillance or COMPASS or Uppsala Monitoring).tw.
157. (Saskhealth or Quebec medical claims database or Regie de l'assurance-maladie du Quebec or RAMQ or Nova Scotia Pharmacare or (Health Insurance Commission adj Australia) or Intercontinental Marketing Services Health or medwatch or Linked Health Database or BCLHD).tw.
158. (VAERS or Vaccine Adverse Event Reporting System or adverse events reporting system or AERS or Fallon Health Plan or Harvard Pilgrim or Kaiser Permanente or ACOVE or (Assessing Care adj Vulnerable Elders)).tw.
159. (euromedstat group or euro med stat group).au.
160. or/148-159
161. exp hydroxymethylglutaryl coenzyme A reductase inhibitor/
162. exp heptanoic acid derivative/
163. (Statin$ or reductase inhibitor$).tw.
164. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
165. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
166. or/161-165
167. exp omega 3 fatty acid/
168. essential fatty acid/
169. unsaturated fatty acid/
170. linolenic acid/
171. fish oil/
172. (n 3 fatty acid$ or omega 3).tw.
173. eicosapenta?noic.tw,hw.
174. docosahexa?noic.tw,hw.
175. alpha linolenic.tw,hw.
176. (linolenate or cervonic or timnodonic).tw,hw.
177. (mediterranean adj diet$).tw.
178. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
179. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
180. (fish adj2 oil$).tw.
181. (cod liver oil$ or marine oil$ or marine fat$).tw.
182. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
183. (fish consumption or fish intake or (fish adj2 diet$)).tw.
184. or/167-183
185. Bile Acid Sequestrant/
186. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
187. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
188. colestyramine/
189. colestipol/ or colestilan/
190. (colestimide or colestilan or colestipol).tw.
191. or/185-190

192. ezetimibe.mp.
193. 163222-33-1.rn.
194. (cholester$ adj3 inhibit$).tw.
195. or/192-194
196. (fibrate$ or fibric acid$).tw.
197. clofibric acid/
198. clofibrate/
199. bezafibrate/
200. gemfibrozil/
201. fenofibrate/
202. ciprofibrate/
203. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
204. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
205. or/196-204
206. nicotinic acid/
207. (niacin or nicotinic acid).tw.
208. or/206-207
209. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
210. drug combination/
211. (combination adj3 therapy).tw.
212. add-on therapy.tw.
213. or/210-212
214. 166 and (or/184,191,195,205,208-209,213)
215. or/122,147,160
216. 214 and 215
217. limit 216 to review
218. 216 not 217
219. limit 218 to (english and human and yr=2008-2011)
220. lancet.jn.
221. ("jama journal of the american medical association" or "jama the journal of the american medical association").jn.
222. "annals of internal medicine".jn.
223. (bmj or bmj clinical research ed).jn.
224. "new england journal of medicine".jn.
225. "american journal of cardiology".jn.
226. circulation.jn.
227. (atherosclerosis or atherosclerosis supplements).jn.
228. clinical chemistry.jn.
229. ("current medical research and opinion" or "current medical research and opinion supplement").jn.
230. or/220-229
231. 219 and 230
232. 231 use emez
233. 116 or 232
234. remove duplicates from 233
235. 234 use prmz

236. 234 use emez

****

MEDLINE – No Date or Filters

Time period covered: 2008 to October 27, 2011

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1948 to October 27 2011>

1. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/
2. Heptanoic Acids/
3. (Statin$ or reductase inhibitor$).tw.
4. (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin).mp.
5. (110862-48-1 or 287714-41-4 or 75330-75-5 or 79902-63-9 or 81093-37-0 or 93957-54-1).rn.
6. or/1-5
7. exp fatty acids, omega-3/
8. fatty acids, essential/
9. Dietary Fats, Unsaturated/
10. linolenic acids/
11. exp fish oils/
12. (n 3 fatty acid$ or omega 3).tw.
13. eicosapenta?noic.tw,hw,rw.
14. docosahexa?noic.tw,hw,rw.
15. alpha linolenic.tw,hw,rw.
16. (linolenate or cervonic or timnodonic).tw,hw,rw.
17. (mediterranean adj diet$).tw.
18. ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) adj2 oil$).tw.
19. (walnut$ or butternut$ or soybean$ or pumpkin seed$).tw.
20. (fish adj2 oil$).tw.
21. (cod liver oil$ or marine oil$ or marine fat$).tw.
22. (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov$).tw.
23. (fish consumption or fish intake or (fish adj2 diet$)).tw.
24. or/7-23
25. (anticholesteremic resin$ or (bile adj3 resin$) or BAR or BAS or Sequestrant$ or Bile acid$).tw.
26. (cholestyramine or colestyramin$ or quantalan or questran or colesevelam).tw.
27. Cholestyramine Resin/
28. Colestipol/
29. (colestimide or colestilan or colestipol).tw.
30. or/25-29
31. ezetimibe.mp.
32. 163222-33-1.rn.
33. (cholester$ adj3 inhibit$).tw.
34. or/31-33

35. (fibrate$ or fibric acid$).tw.
36. Clofibric acid/
37. Clofibrate/
38. Bezafibrate/
39. Gemfibrozil/
40. Fenofibrate/
41. (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate).tw.
42. (637-07-0 or 25812-30-0 or 41859-67-0 or 882-09-7 or 49562-28-9).rn.
43. or/35-42
44. niacin/
45. nicotinic acid/
46. niacin.tw.
47. or/44-46
48. (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite).mp.
49. Drug Therapy, Combination/
50. (combination adj3 therapy).tw.
51. add-on therapy.tw.
52. or/49-51
53. 6 and (or/24,30,34,43,47-48,52)
54. or/24,30,34,43,47-48,52
55. exp Cardiovascular Diseases/
56. 54 and 55
57. or/6,56
58. limit 57 to systematic reviews
59. limit 57 to meta analysis
60. or/53,58-59
61. limit 60 to english
62. limit 61 to yr="2008 -Current"
63. lancet.jn.
64. jama.jn.
65. "annals of internal medicine".jn.
66. bmj.jn.
67. "new england journal of medicine".jn.
68. american journal of cardiology.jn.
69. circulation.jn.
70. (atherosclerosis or atherosclerosis supplements).jn.
71. clinical chemistry.jn.
72. current medical research & opinion.jn.
73. or/63-72
74. 62 and 73

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#1 MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees

#2 MeSH descriptor Heptanoic Acids explode all trees

#3 (Statin* or (reductase NEXT inhibitor*)):ti,ab,kw

#4 (Simvastatin or Atorvastatin or Rosuvastatin or Pravastatin or Lovastatin or Fluvastatin or Mevastatin or Pitavastatin):ti,ab,kw

#5 ("110862-48-1" or "287714-41-4" or "75330-75-5" or "79902-63-9" or "81093-37-0" or "93957-54-1"):ti,ab,kw

#6 (#1 OR #2 OR #3 OR #4 OR #5)

#7 MeSH descriptor Fatty Acids, Omega-3 explode all trees

#8 MeSH descriptor Fatty Acids, Essential explode all trees

#9 MeSH descriptor Dietary Fats, Unsaturated explode all trees

#10 MeSH descriptor Linolenic Acids explode all trees

#11 MeSH descriptor Fish Oils explode all trees

#12 (("n 3 fatty" NEXT acid*) or "omega 3"):ti,ab,kw

#13 (eicosapentanoic or eicosapentaenoic):ti,ab,kw

#14 (docosahexanoic or docosahexaenoic):ti,ab,kw

#15 ("alpha linolenic"):ti,ab,kw

#16 (linolenate or cervonic or timnodonic):ti,ab,kw

#17 (mediterranean NEXT diet*):ti,ab,kw

#18 ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed) NEAR/2 oil*):ti,ab,kw

#19 (walnut* or butternut* or soybean* or (pumpkin NEXT seed*)):ti,ab,kw

#20 (fish NEAR/2 oil*):ti,ab,kw

#21 (("cod liver" NEXT oil*) or (marine NEXT oil*) or (marine NEXT fat*)):ti,ab,kw

#22 (salmon or mackerel or herring or tuna or halibut or seal or seaweed or anchov*):ti,ab,kw

#23 ("fish consumption" or "fish intake" or (fish NEAR/2 diet*)):ti,ab,kw

#24 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23)

#25 ((anticholesteremic NEXT resin*) or (bile NEAR/3 resin*) or BAR or BAS or Sequestrant* or (Bile NEXT acid*)):ti,ab,kw

#26 (cholestyramine or colestyramin* or quantalan or questran or colesevelam):ti,ab,kw

#27 MeSH descriptor Cholestyramine Resin explode all trees

#28 MeSH descriptor Colestipol explode all trees

#29 (colestimide or colestilan or colestipol):ti,ab,kw

#30 (#25 OR #26 OR #27 OR #28 OR #29)

#31 ezetimibe:ti,ab,kw

#32 "163222-33-1":ti,ab,kw

#33 (cholester* NEAR/3 inhibit*):ti,ab,kw

#34 (#31 OR #32 OR #33)

#35 (fibrate* or (fibric NEXT acid*)):ti,ab,kw

#36 MeSH descriptor Clofibric Acid explode all trees

#37 MeSH descriptor Clofibrate explode all trees

#38 MeSH descriptor Bezafibrate explode all trees

#39 MeSH descriptor Gemfibrozil explode all trees

#40 MeSH descriptor Fenofibrate explode all trees

#41 (gemfibrozil or fenofibrate or bezafibrate or clofibrate or clofibric acid or procetofen or ciprofibrate):ti,ab,kw

#42 ("637-07-0" or "25812-30-0" or "41859-67-0" or "882-09-7" or "49562-28-9"):ti,ab,kw

#43 (#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42)

#44 MeSH descriptor Niacin explode all trees

#45 MeSH descriptor Nicotinic Acids explode all trees

#46 niacin:ti,ab,kw

#47 (#44 OR #45 OR #46)

#48 (Zetia or Lopid or Tricor or Lofibra or Welchol or Colestid or Questran or Prevalite):ti,ab,kw

#49 MeSH descriptor Drug Therapy, Combination explode all trees

#50 (combination NEAR/3 therapy):ti,ab,kw

#51 "add-on therapy":ti,ab,kw

#52 (#49 OR #50 OR #51)

#53 (#6 AND (#24 OR #30 OR #34 OR #43 OR #47 OR #48 OR #52))

#54 (#53), from 2

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) specifies findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B: Updating Signals (Continued)

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
Key Question # 1: Comparative long-term benefits and rates of serious adverse events of coadministration of different lipid-modifying agents (i.e., a statin plus another lipid-modifying agent) compared with higher dose statin monotherapy?						
ACCORD Study Group, 2010 [15]	RCT	5518 pts with type 2 diabetes; Mean age: 62.3±6.8; Male: 69.3%	Fenofibrate (160mg) +statin (dose:NR) (;n= 2765)vs. statin (dose:NR) (;n= 2753)	4.7 yrs (mean)	Fatal/ nonfatal cardiovascular event, Nonfatal (myocardial infarction, Stroke)	<u>Fenofibrate +statin vs. statin</u> **Rate of fatal/nonfatal cardiovascular event:** 2.24 vs. 2.41; p= 0.32 HR: 0.92, 95% CI(0.79, 1.08) **Rate of major coronary disease event:** 2.58 vs. 2.79, p=0.26 HR: 0.92, 95% CI(0.79, 1.07) **Rate of nonfatal myocardial infarction** 1.32 vs. 1.44, p=0.39 HR: 0.91, 95% CI (0.74, 1.12) **Rate of Stroke** **Any:** 0.38 vs. 0.36, p=0.80 HR: 1.05, 95% CI (0.71, 1.56) **Nonfatal** 0.35 vs. 0.30, p=0.48 HR: 1.17 (0.76, 1.78) **Rate of Death** **Any cause** 1.47 vs. 1.61, p=0.33 HR: 1.61, 95% CI(0.75, 1.10) **Cardiovascular** 0.72 vs. 0.83, p=0.26 HR: 0.86, 95% CI (0.66, 1.12)

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						Rate of fatal/nonfatal congestive heart failure 0.90 vs. 1.09, p= 0.10 HR: 0.82, 95% CI (0.65, 1.05)
Boden, 2011[24]	RCT	3414 pts with established cardiovascular diseases; Mean age: 63.7±8.8; Male: 85.2%	[Extended –release niacin (1500-2000mg/day); n= 1718] + Simvastatin (40-80mg/day)] vs. [placebo + Simvastatin (40-80mg/day); n=1696]	36 months	Composite death from coronary heart disease, nonfatal MI, ischemic stroke, and hospitalization for ACS, or symptom-driven coronary or cerebral revascularization	<u>Placebo+ Statin vs. Extended-release niacin</u> **Composite death:** HR: 1.02, 95%CI (0.8-1.21); p= 0.80 **Death from CHD, nonfatal MI,high-risk ACS or ischemic stroke:** HR: 1.08, 95%CI (0.87-1.34); p=0.49 **Death from CHD, nonfatal MI or ischemic stroke:** HR: 1.13, 95%CI (0.90- 1.42); p=0.30 **All deaths from cardiovascular causes:** HR: 1.17, 95%CI (0.76- 1.80); p=0.47 **Death from CHD:** HR: 1.10, 95%CI (0.69- 1.75); p=0.68 **Death from any causes:** HR: 1.16, 95%CI (0.87- 1.56); p=0.32 **Nonfatal MI:** HR: 1.11, 95%CI (0.84- 1.47); p=0.46 **Ischemic stroke:** HR: 1.61, 95%CI (0.89- 2.90); p=0.11 **Ischemic stroke or stroke of uncertain origin:** HR: 1.67, 95%CI (0.93- 2.99); p=0.09
Key question # 2: Do these regimens differ in reaching LDL targets (or other surrogate markers), short-term side effects, tolerability, and/or adherence?						
Boden, 2011[24]	RCT	3414 pts with established cardiovascular diseases; Mean age: 63.7±8.8;	[Extended –release niacin (1500-2000mg/day); n= 1718] + Simvastatin (40-80mg/day)] vs. [	36 months	Composite death from coronary heart disease,	<u>Placebo+ Statin vs. Extended-release niacin+ statin</u> **Median LDL-c (mg/dl) change from baseline (%):** -7.6 vs. -13.6; p=NR **Median HDL-c (mg/dl) change from baseline (%):** 11.8 vs. 25.0; p=NR

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
		Male: 85.2%	placebo + Simvastatin (40-80mg/day); n=1696]		nonfatal MI, ischemic stroke, and hospitalization for ACS, or symptom-driven coronary or cerebral revascularization	**Mean HDL –c (mg/dl) change (baseline vs. final follow up in combination arm):** 34.8±5.9 vs. 44.1±11.3 **Mean HDL –c (mg/dl) change (baseline vs. final follow up in monotherapy arm):** 35.3±5.9 vs. 39.1±7.7 ;p=NR **Discontinuation of study drug after randomization- no (%):**341 (20.1) vs. 436 (25.4); p<0.001 **Abnormality on liver- function test:** 5(0.3) vs. 5 (0.3);p=NR
West, 2011[5]	RCT	67 pts with PAD; Mean age: 63±10; Male:55%	Statin naïve & statin + ezetimibe 10mg;n=(33)	2 yrs	LDL-C ; plaque volume; plaque parameters	<u>simvastatin + ezetimibe vs. simvastatin for statin naïve group:</u> **LDL-C at Baseline:** (118±9 mg/dl) vs. (118±10 mg/dl); p=NR **LDL-C at year 1** (67±7 mg/dl) vs. (91±8 mg/dl); p < 0.05 **LDL-C at year 2** 68±10 mg/dl vs. 83 ±11 mg/dl **HDL-C at Baseline:** (48±4 mg/dl) vs. (45±4 mg/dl); p=NR **HDL-C at year 1** (42±3 mg/dl) vs. (46±3 mg/dl); p =NR **HDL-C at year 2** (46±3 mg/dl) vs. (44 ±4 mg/dl);p=NR

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						Plaque volume: baseline vs. year2 11.5 ±1.4 cm3 - 10.5±1.3 cm3 ; p= NS 11.0 ±1.5 cm3 –10.5±1.4 cm3 ; p= NS <u>In statin + ezetimibe:</u> **LDL-C at baseline vs. year 1 vs. year 2** 100±4 vs. 80± 6* 77 vs. 77±5; p<= 0.05 **Plaque volume: baseline vs. year2** 10.0 ± 0.8 vs. 10.8 ± 0.9; p < 0.01
Mikhailidis, 2011[8]	Meta Analysis of Review of RCTs	5080 pts with CHD, high risk for CHD, Diabetes & Hypercholestremia ; Mean age: NR; Male: NR	ezetimib 10mg/day + statin (10-80mg/day ; n=2573) vs. statin (10-80mg/day; n= 2507)	6 wk- 48 wk	mean percentage change in LDL-C, HDL-C & achieving LDL-C treatment goal	<u>Statin+ezetimib vs. statin monotherapy</u> **WMD in LDL-C:** -14.1% (-16.1, -12.1); p<0.001 <u>Statin+ezemitib vs. statin titration</u> **Achievement of LDL-C goal:** OR: 2.45; 95% CI (1.95, 3.08); p = 0.007 <u>Ezetimibe+statin vs. statin fixed- and random-effects meta-analyses</u> **Pooled effect estimate (%)** **(95% CI) WMD or OR** **LDL-c:** -14.1 (-16.1, -12.1); p<0.001; I2 % : 65.8; Heterogeneity p= 0.001

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						LDL-c treatment goal: 2.38 (1.89, 2.98);p<0.001; I^2 %:55.4; Heterogeneity p= 0.020 **HDL-c**: 1.8 (1.0, 2.6); p<0.001; ; I^2 %:<1.0; Heterogeneity p= 0.818 **T/ HDL-c**:- 10.8 (-12.4, -9.2); p<0.01; I^2 %: 18.7; Heterogeneity p= 0.287
Zieve, 2010 [20]	RCT	1053 pts at high risk of CHD; Mean age: 71±5 yrs; Male: 46.5%	[Atrovastatin (10mg/day) + Ezetimib (10mg) ; n=526] vs. Atorvastatin (20/40 mg/day; n=527)	12 wk	LDL percentage change; tolerability	Atrovastatin + Ezetimib vs. Atrovastatin **LDL (mg/dl) mean % change** **Wk 6**: -14, 95% CI (16; -12); p<0.001 **Wk 12**:-5, 95% CI (-7, -2); p=0.001 **HDL (mg/dl) mean % change** **Wk 6**: 2, 95% CI (0.3, 4); p=0.021 **Wk 12**: 3, 95% CI (2,5);p< 0.001 **TC/HDL ratio (mg/dl) mean % change** **Wk 6**: -9, 95% CI (-11, -7); p<0.001 **Wk 12**: -5, 95% CI (-7, -2); p<0.001 **Tolerability**: Comparable in both groups **Adverse Event n (%)** Atrovastatin 10+ Ezetimib 10 vs. Atrovastatin 20/40 Drug related: 30 (6%) vs. 26 (5%)

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						Serious: 15 (3%) vs. 14 (3%) Serious drug related: 1 (<1%) vs. 0 Discontinuations Drug related; 6 (1%) vs. 3 (1%) Discontinuations Drug related Serious: 4 (1%) vs. 3 (1%) AST≥ 3x upper lmit of normal: 1/520 (<1%) vs. 3/520 (1%); p>0.05 ALT≥ 3x upper limit of normal: 2/520 (<1%) vs. 5/520 (1%); p>0.05
Goldberg, 2011 [12]	RCT	1393 pts with mixed dyslipidemia; 56.5 ± 10.32 Mean age: ; Male: 0%	[Fenofebric acid (10mg)+ low dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg);n=263] vs. [low dose statin (rosuvastatin 10 mg, simvastatin 20 mg, or atorvastatin 20 mg);n=234	18wk	Not clear	<u>Fenofebric acid + low dose statin vs. low dose statin</u> **HDL-c level incensement:** 20% vs. 8% ;p=NR **LDL-c level reduction:**37% vs. 36%;P=NR **Adverse Events- n (%):** **Serious: 8 (3) vs. 4 (2)** **Leading to discontinuation:** 36 (14) vs. 11 (5) **Any treatment related:** 75 (29) vs. 43 (18) **Myalgia:** 8 (3) vs. 4 (2) **ALT incidence≥ 3x ULN:**5 (2%) vs.0; p=NR **AST incidence≥ 3 x ULN**:2 (1%) vs. 0; p=NR

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
			And [Moderate-dose statin (rosuvastatin 20 mg, simvastatin 40 mg, or atorvastatin 40 mg); n = 249] vs. [fenofibric acid + moderate-dose-statin; n= 245]			**CPK≥ 10 x ULN**: 0 vs. 0; p=NR <u>Fenofebric acid +moderate dose statin vs. moderate dose statin</u> **LDL-c level reduction**:39% vs. 43%;p=NR **ALT incidence≥ 3x ULN**:5 (2%) vs. 0 **AST incidence≥ 3 x ULN**:2 (1%) vs. 0
Bozzetto, 2011[6]	RCT Crossover	15 diabetic pts; Mean age:55±5 yrs; Male:80%	(Ezetimibe 10mg+ simvastatin 20mg; n=15) vs. (placebo + simvastatin 20mg ; n=15)	6 wk	Lipoprotein profile in fasting and postprandial	<u>Ezetimibe+Statin vs. Statin</u> **LDL (mg/dl) difference from baseline:**-88± 21 vs. -70±20; p<0.005 **HDL (mg/dl) difference from baseline**:-1.6±4 vs.-1.2±6; p:NR
Bays, 2011[7]	RCT	440 pts with moderately high/high risk of coronary heart disease; Mean age: 61 yrs; Male: 62%	[Ezetimibe (10 mg)+ rosuvastatin (5,10)mg; n=99 & 122] vs. [up-titration of rosuvastatin (10,20)mg; n=98,121)]	6 wk	LDL percentage change from baseline; LDL target achievement	<u>Ezetimibe (10 mg)+ rosuvastatin (5mg) vs. rosuvastatin (10mg)</u> **LDL percentage change**-12.3 ; p<0.001 **HDL percentage change**-4.5 ; p=0.017 **T/HDL ratio percentage change**-1.4; p=NR <u>Ezetimibe (10 mg)+ rosuvastatin (10mg) vs. rosuvastatin (20mg)</u> **LDL percentage change:**-17.5; p<0.001 **HDL percentage change**:-0.3;p=NR

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						T/HDL ratio percentage change: -10.6; p<0.001 **Adverse events:** All rosuvastatin 5,10 +Ezetimib10 vs. All rosuvastatin 10,20: n (%); Difference (95%CI) **Serious Drug-related**: 10 (4.5%) vs. 6 (2.7%); 1.8 (-1.9, 5.7) **Serious**: 0 vs. 2 (0.9%); -0.9 (-3.3, 0.8) **Discontinuations Drug-related**: 5 (2.3%) vs. 0; 95% CI:NR **AST & ALT ≥ 3upper limit**: 1/219 (0.5%) vs. 0/214; 0.5 (-1.3, 2.5); p= 0.327 **Adverse effects ≥1 Events:** 33 (14.9%) vs. 31 (14.2%); 0.8 (_5.9, 7.5)
Azar, 2011 [9]	RCT	100 pts with CAD; Mean age: 64.5±9.5; Male: 85%	(Ezemitib 10mg/day +Atorvastatin 40mg/day; n=50) vs. (Atorvastatin 40mg/day+placebo; n=50)	8 wk	Effect of treatment on phospholipase A2	Ezemitib +Atorvastatin vs. Atorvastatin+ placebo **LDL(mg/dl) baseline vs. final** (102±29 vs. 77±10; p<0.001) vs. (99±21 vs. 86±14;P<0.001); p=NS; p<0.001 **HDL(mg/dl) baseline vs. final** (37±8 vs. 38±7; p=NS) vs. (37±8 vs. 37.9;p=NS);p=NS; p=NS
Foody, 2010 [10]	RCT	1289 hypercholostremic pts; Mean age: 71.98 yrs; Male: 37.2%	1- (Ezemitib 10mg+ simvastatin 20mg vs. Atorvastatin 10mg) 2- (Ezemitib 10mg+ simvastatin 20mg vs. Atorvastatin 20mg) 3- (Ezemitib10mg+ simvastatin 40mg vs.	12 wk	LDL Mean % change from baseline	Treatment differences: (Ezemitib 10mg+ simvastatin 20mg vs. Atorvastatin 10mg) **LDL :-**14.7; p<0.001 **HDL:** 2.4; p=NR **TC/HDL:** -10.8; P<0.001 (Ezemitib 10mg+ simvastatin 20mg vs. Atorvastatin 20mg)

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
			Atorvastatin 40mg)			**LDL:-**7.5; p<0.001 **HDL**:3.3; p<0.05 **TC/HDL:** -6.2; P<0.001 Ezemitib10mg+ simvastatin 40mg vs. Atorvastatin 40mg **LDL:-**8.2;p<0.001 **HDL:**2.1;p=NR **TC/HDL**: -6.9;P<0.001
Florentin, 2011 [11]	RCT	100 pts with hypercholestremia; Mean age: 58±9.5; Male: 67%	(Simvastatin 10mg + ezetimibe 10mg; n=50) vs. (Simvastatin 40mg; n=50)	3 months	LDL-C level	Simvastatin+Ezemitib vs. Simvastatin: **LDL-C mg/dL % Change**: -49 vs. -43; p<0.0001 **HDL-C mg/dL % Change**: 0.3 vs. 0.3; p=NR **TC/HDL-C mg/dL % Change**: -35 vs. -31; p<0.0001
Enger, 2010[13]	Non RCT	584,784 pts initiated Statin or fibrates; Mean age:NR; Male: 57.4%	[Statin +Fibrate initiators (dose:NR) ;n=3515] vs. [Statin Initiators(dose:NR); n= 507932)]	2004- 2007	Hospitalization for rhabdomyolysis, renal impairment, hepatic injury, or pancreatitis	(Statins and fenofibrate); (Statins and gemfibrozil); Statins only **Rhabdomyolysis:** Adjusted IRR (95% CI):3.75 (1.23–11.40) **Myopathy: IR/ 100,000 patient-years, 95% CI** 3.75 (0.34, 17.48); 41.40(8.26; 132.70); 1.76(0.83; 3.32) **Renal impairment : IR/ 100,000 patient-years, 95% CI** 226.38(174.39, 289.98); 249.58 (136.29, 422.73); 108.87 (99.59, 118.79) **Renal failure requiring renal replacement: IR/ 100,000 patient-years, 95% CI** 52.82(30.25,86.26); 62.40(17.27,166.47);26.67(22.23, 31.74) **Hepatic injury:** IR/ 100,000 patient-years, 95% CI 11.25(3.11, 30.02); 20.69(1.88,96.47); 8.57(6.19, 11.59) **Pancreatitis:** IR/ 100,000 patient-years, 95% CI 157.94(115.41, 211.34); 83.11(27.78, 197.57)

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
Costet, 2010 [14]	RCT, Cross over	26 diabetic pts; Mean age: 57±7 yrs; Male:73%	[Fenofibrate (160mg)+Atorvastatin (10mg) ; N=26] vs. [Atorvastatin (10mg)]	6 weeks	LDL	Baseline vs. 6 weeks (mg/dl) Fenofibrate +Atorvastatin : **LDL:** 109±35 vs. 90±25;p=0.003 **HDL:** 48±13 vs. 48±13; p=0.006 Atorvastatin **LDL**:144±33 vs. 100±27; p<0.001 **HDL:** 45±13 vs. 46±11; p=NR
Farnier, 2010[17]	RCT	248 pts with mixed hyperlipidemia; Mean age: 58±9; Male: 70.2%	[Fenofibrate (160 mg) ± Pravastatin (40 mg);n= 123] vs. [Pravastatin (40 mg);n=125]	12 wk	LDL, HDL	Fenofibrate +Pravastatin vs. Parvastatin **Mean % change (mg/dl)** **LDL:** -11.7 vs.-5.9; p= 0.019 **HDL:** 6.5 vs. 2.3; p= 0.009 **Incidence of adverse events- n(%):** Serious drug-related adverse event: 1 (0.8) vs. 0 **AST and ALT≥3 x ULN:** 0 vs. 0
Azar, 2010[18]	RCT	100 pts with CHD or CHD equivalent; Mean age: 64.5±9.9; Male: 85%	[Ezetimibe (10 mg) + atorvastatin (40 mg); n=50] vs. [atorvastatin (40 mg); n=50]	8wk	LDL	Ezetimibe + atorvastatin vs. atorvastatin **LDL(mg/dl)** **Baseline:** 102±29 vs. 99± 21; p=NS **Final:** 77±10 vs.86±14; p<0.001 **HDL(mg/dl)** **Baseline**: 37±8 vs. 37±8; p=NS **Final**: 38±7 vs. 37±9;p=NS
Maki, 2010[19]	RCT	256 subjects; Mean age:59.8 yrs; Male: 57.5%	[Omega-3 acid ethyl ester (P-OM3) (4g/day) + Simvastatin (40 mg/day); n=122] vs. simvastatin (40	8 wk	HDL	P-OM3+ Simvastatin vs. Simvastatin +Placebo **% Change in HLDL (mg/dl)** **For LDL< 80.4**: 4(0,22) vs. -1(-7, 5) **For LDL< 80.4 - <99.0**: 2(-4,7) vs. -1(-9,6)

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
			mg/day)+placebo;n=132]			**For LDL >=90**: 4(-3,13) vs. -1(-5,2)
Derosa, 2009[21]	RCT	241 pts with diabetes type 2; Mean age: 51.10yrs; Male: 49%	[fenofibrate (145 mg/day) + simvastatin (40 mg/day);n=79] vs. [simvastatin (40 mg/day);n=82]	12 months	Not clear	Fenofibrate+ simvastatin vs. simvastatin **Baseline vs. 12 months (mg/dl)** **LDL-C:** (188±17 vs.184±19) vs. (112±14 vs. 142±17);p<0.001 **HDL-C**: Baseline (41± 9 vs. 46±9.5);p=NR vs. 12 months (55±11 vs. 51±7.5); p<0.001
Robinson, 2009[22]	RCT	1128 pts with hypercholestremia & Metabolic syndrome; Median age: 59 yrs; Male; 56.4%	1- (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 10mg) 2- (Ezemitib 10mg+ Simvastatin20mg vs. Atorvastatin 20mg) 3- (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg)	6 wk	LDL Mean % change from baseline	Treatment differences: (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 10mg) **LDL-C** :-13.1; p<0.001 **HDL-C**: 3.4; p=0.05 **T/HDL-C**: -8.8; p<0.001 (Ezemitib 10mg+ Simvastatin 20mg vs. Atorvastatin 20mg) **LDL-C**:-10.2; p<0.001 HDL-C:1.2;p=NR **T/HDL-C**: -5.3; p<0.001 (Ezemitib10mg+ Simvastatin 40mg vs. Atorvastatin 40mg) **LDL-C**:-8.0; p<0.001 **HDL-C**:4.0;p<0.01 **T/HDL-C**: -5.9; p<0.001

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						Adverse events: **All Atorvastatin n(%) vs. All Ezemitib / Simvastatin n(%); Difference (95%CI)** **Drug-related:** 26 (3.8) vs. 15 (3.3); -0.5 (-2.7, 1.9) **Serious:** 9 (1.3) vs. 1 (0.2); -1.1 (-2.3, 0.0) **Serious drug-related**: 1 (0.1) vs.0; -0.1 (-0.8, 0.7) **Discontinuation Drug-related**: 7 (1.0) vs. 4 (0.9); -0.1 (-1.4, 1.3) **Discontinuation serious Drug-related:** 1 (0.1) vs. 0; -0.1 (-0.8, 0.7) **Rate of ALT≥3xULN** 2 (0.3%) vs. 1 (0.2%); -0.1 (-0.9, 1.0); p=0.81 **Rate of AST≥ 3xULN** 1 (0.2%) vs. 5 (1.1%); 1.0 (0.1, 2.5); p=0.03 **Rate of CPK≥ 10xULN** 0 vs. 1 (0.2%); 0.2 (-0.4,1.3); p=0.22
Briseno, 2010[23]	Non RCT	187 pts with dyslipidemial\ (29% diabetic); Mean age: 64.47 yrs; Male: 65.58%	[ezetimibe/simvastatin (10/20mg/day);n=89] vs. [rosuvastatin (10mg/day);n=98]	Jan 2004-Dec 2005	LDL-c goal	ezetimibe/simvastatin vs. rosuvastatin **LDL-c goal achievement (2001 and 2004):** (58.4% vs. 81.4%; p<0.01 and 46.4% vs. 31.5%; p<0.01) **Least-squares mean % change inLDL-C from baseline:** -35 vs. -46.7; p<0.001
Key question # 3: Compared with higher dose statins and to one another, do combination regimens differ in benefits and harms within subgroups of patients?						
ACCORD Study Group, 2010[15]	RCT	5518 pts with type 2 diabetes; Mean age: 62.3±6.8;	Fenofibrate 160mg +statin; dose:NR (;n= 2765)vs. statin;	4.7 yrs (mean)	Fatal/nonfatal cardiovascular event,	Fenofibrate +statin vs. statin

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
		Male: 69.3%	dose:NR(;n= 2753)		Nonfatal(myocardial infarction, Stroke)	**Interaction in sex:** **Primary outcome in Female (% of events)** :9.05 vs. 6.64 **Primary outcome in Male (% of events)** :11.18 vs. 13.30 P=0.001 for interaction **Mean LDL-C (mg/dl):(baseline vs. baseline) vs. (end of follow vs. end of follow up):**(100.0 vs. 101.1; p=0.16) vs. (81.1vs. 80.0; p=0.16) **Mean HDL –c (mg/dl): (baseline vs. baseline) vs. (end of follow vs. end of follow up):**(38.0 vs. 38.2; p=0.27) vs. (41.2vs. 40.5; p=0.01) **Serious Adverse Events n (%):** **severe muscle aches/pains not associated with known activities; n(%):** 1110 (40.1) vs. 1115 (40.5);p= 0.79 **Rhabdomyolysis ; n (%):** 4 (0.1) vs. 3 (0.1); p= 1.00 **ALT ever ≧ 3x ULN n(%);** 52 (1.9) vs. 40 (1.5);p= 0.21 **CPK ever ≧ 10x ULN ; n(%):** 10 (0.4) vs. 9 (0.3); p= 0.83
ACCORD Study Group, 2010[16]	RCT	1593 pts with type 2 diabetes and at risk of cardiovascular disease; Mean age: 61.5±6.5; Male: 31%	[Fenofibrate (160mg)+Simvastatin(dose:NR);N=806] vs. [Simvastatin(dose:NR) +placebo ;n=787]	4 years	Progression of diabetic Retinopathy	Fenofibrate+Simvastatin vs. Simvastatin+placebo **Median HDL(mg/dl)** (Baseline vs. 1year: 38 vs. 40) vs. (38 vs.39); p=0.002 **Median LDL (mg/dl)**(Baseline vs. 4 year: 93 vs. 78) vs. (Baseline vs. 4 year: 93 vs. 78);p=0.68 **Rate of progression of Retinopathy at 4 year:** 6.5% (52/806) vs. 10.2% (80/787). Adjusted ORl 0.60; 95%CI (0.42, 0.87); p=0.006 **Rate of moderate vision loss:**

Author year Study name (if applicable)	Study design	participants	Intervention groups (dose;n)	Treatment duration	outcome	Findings
						23.7% (227/956) vs. 24.5% (233/950); Adjusted HR: 0.95; 955CI (0.79, 1.14); p=0.57
Abbreviations: PAD: peripheral arterial disease; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; WMD: (weighted mean difference; OR: Odd Ration; CI: Confidence Interval; CHD: Coronary Heart Disease ;WK: Week; HR: Hazard Ratio; CAD: Coronary Artery Disease; NS: Not significant; ACS: Acute Coronary Syndrome; MI: myocardial infarction; NR:Not Reported; S: Statin; x ULN: times upper limit of normal; AST: elevated serum aspartate transaminase; ALT: alanine transaminase;CPK: creatinine phosphokinase;NS: Not Significant						

Appendix D: Questionnaire Matrix

Comparative Effectiveness of Lipid-Modifying Agents

AHRQ Publication No. 09-EHC024-EF September 2009

Access to full report: http://www.ncbi.nlm.nih.gov/books/NBK43220/

Clinical expert name: Dr. Teik Chye Ooi

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1. Long-Term Benefits and Serious Adverse Events			
There are several important limitations in the evidence regarding long-term clinical outcomes. Most of the evidence originates from short-term studies aimed at biochemical measures and therefore is insufficient for the clinical events of interest, including the occurrence of MI, stroke, or death. In trials of combination therapy, the monotherapy comparator arms rarely explored higher-dose statins or were not performed in individuals requiring intensive lipid lowering. Due to these limitations in the available data, we present first our results based on the available evidence for the group requiring intensive lipid lowering when combination treatment is compared to a higher dose of a statin, and then provide a broader perspective using available data in all risk groups comparing combination therapy to any monotherapy statin dose.	Yes	No	
All-cause mortality. The quality of evidence was very low for all available comparisons of combinations and	Yes	No	

monotherapy reported below. For individuals requiring intensive therapy, limited evidence was available for statin combinations with ezetimibe and fibrates compared to higher doses of statins. In the two statin-ezetimibe combination trials, no deaths occurred in either the combination or the statin monotherapy group, precluding a comparative analysis of mortality. A single trial with a statin-fibrate combination showed no difference in mortality compared with a higher dose statin. Trials comparing combination therapy with statin monotherapy that were not limited to individuals requiring intensive lipid lowering and did not necessarily compare combination therapy with a higher dose of statin monotherapy were examined for an effect on mortality. No significant differences between treatments were observed across any combination, including ES-5statin-omega-3 combination, which was studied in three trials, one of which was a large trial lasting 5 years of 18,645 Asians. **Vascular death.** Treatments aimed at modifying lipids might be expected to lower the rates of death due to vascular diseases such as heart disease and stroke. However, no trials examined this outcome in a high-risk population and compared the combination to a higher statin dose. Across all available trial populations, two trials each of statin-ezetimibe and statin-niacin combinations did not demonstrate a difference in the occurrence of rare vascular deaths. The quality of evidence was very low for evidence pertaining to both combinations. **Other clinical outcomes.** For the outcomes of reduction of MI or stroke or avoidance of revascularization procedures on the carotid or coronary vessels, no evidence comparing combination therapy with a higher dose of statin was available. Evidence comparing various doses of statin-ezetimibe, statin-fibrate, statin-niacin, and statin-BAS combinations with statin monotherapy was available from	Yes Yes Yes Yes	No No No No	# **ACCORD-LIPID study** (NEJM 2010; 362:1563-1574) shows no effect of adding fenofibrate to simvastatin on mortality and any of the individual secondary clinical endpoints including non-fatal MI. A *a priori* subgroup analysis on a subset with high triglycerides and low HDL-C showed significant reduction in cardiovascular outcomes # **ACCORD-Eye sub-study** (NEJM 2010; 363:233-244) showed that fenofibrate therapy added to simvastatin therapy reduced the risk of and progression of retinopathy and albuminuria (ie. microvascular disease) in patients with type 2 diabetes mellitus. # **AIM-HIGH** study (NEJM Nov 2011; ePub ahead of print) showed no incremental benefit from addition of niacin

few trials registering rare events, and no significant difference was detected. One large statin-omega-3 trial of 18,645 Asians demonstrated no significant difference between treatments for the outcomes of nonfatal MI, hemorrhagic stroke, ischemic stroke, and all stroke over a period of 5 years. **Serious adverse events.** The quality of evidence was very low for all available combination and monotherapy comparisons. Evidence pertained to all available trial populations and not specifically those in need of intensive treatment. Evidence comparing a combination with a higher dose of statin monotherapy was available only for the statin-ezetimibe combination. Three trials with a maximum duration of 24 weeks demonstrated no difference in the rate of serious adverse events. Overall, 5 percent of participants had an event. When various doses and statin types in combinations were compared with statin monotherapy, no significant differences were noted across all combinations, including evidence that combined 27 statin-ezetimibe trials with over 13,000 participants. Absolute rates of serious adverse events varied between 2 and 4 percent. Even across all combinations, no differences were detected when analyses were restricted to the few long-term trials of 24 to 52 weeks duration. **Cancer.** Evidence pertained to all available trial populations and not only those in need of intensive treatment. Some data were available for individuals at any risk level and statin dose. One 5-year omega-3 trial of 18,645 participants demonstrated no significant difference in the incidence of cancer, with an overall rate of 3 percent. With two 24-48-week statin-ezetimibe trials of 971 participants, the rate of incident cancer was 1 percent, with no significant difference between treatments. Cancer was too rare in a single small statin-niacin trial to permit any conclusion. No evidence was available for statin-fibrate and statin-BAS combinations. While the available data do	Yes	No	to statin therapy. # **SHARP study** (Lancet 2011;377:2181-2192) showed that simvastatin plus ezetimibe reduced incidence of major atherosclerotic events in a wide range of patients with chronic kidney disease. (**Note:** I have not provided my personal views and interpretations of the above studies)

not suggest an increased incidence of cancer with ezetimibe or omega-3 combinations, the power to detect small differences in the rates of conditions, such as cancer which may have a long latency prior to presentation, is limited given the current data			
Key Question 2. LDL-c Targets, Short-Term Side Effects, Tolerability, and Adherence			
Surrogate markers are biological markers that are linked to the occurrence of disease and used as targets for therapy. The NCEP ATP report sets treatment goals for various risk categories. In this report, we examine the proportion of individuals attaining the LDL-c goals set by the ATP III panel, the effect on LDL-c and HDL-c levels, the total cholesterol:HDL-c ratio, and markers of atherosclerosis. **Participants attaining ATP III LDL-c goals.** The available evidence is of very low quality for all comparisons of combination with monotherapy. For individuals requiring intensive therapy, two trials employing fixed dose or titrations could be statistically combined. Compared with a higher dose statin alone, statin-ezetimibe combination demonstrated a greater probability of reaching treatment goals. A single trial using a statin-fibrate combination demonstrated no significant difference in the number of participants reaching goals compared to a higher dose statin. No evidence comparing higher dose statin monotherapy with any of the remaining combinations was available for participants requiring intensive treatment. Substantially more information was available for statin-ezetimibe combination therapy in which the treatment comparison was not necessarily a higher dose of statin. In 88 percent of 18 trials conducted in a population in need of intensive treatment, combination therapy was more likely than statin monotherapy to help participants reach LDL-c targets. Likewise, 96 percent of 23 trials favored the statin-ezetimibe combination when all trial populations using various statins as the two treatments were included. No evidence was available for the statin-omega-3 combination. Sparse evidence precluding meaningful	Yes Yes	No No	

conclusions was identified for statin-fibrate (two trials), statin-niacin (one trial), and statin-BAS (one trial) combinations across various doses and populations. **LDL-c.** When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either insufficient or absent for statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations. Scant evidence from two statin-ezetimibe trials was not statistically combined because of heterogeneity, but both trials indicated significant additional reductions of 10 to 20 percent favoring statin-ezetimibe combination therapy over monotherapy. More data were observed for individuals requiring intensive therapy when combinations were compared with any dose of statin. Substantial heterogeneity precluded statistical analysis of 18 statin-ezetimibe and 4 statin-BAS trials. However, all statin-ezetimibe trials favored combination treatment, with mean additional reductions of 4 to 27 percent. Inconsistent results were found for statin-BAS trials, while evidence was insufficient for statin-niacin, statin-BAS, and statin-omega-3 combinations. Across all trial populations, when lower doses of statins in combination were compared with higher doses of the same statin monotherapy, significant additional LDL-c reductions of 3 to 20 percent were observed with statin-ezetimibe combinations (six trials); however, heterogeneity precluded a statistical estimate. Evidence was insufficient or absent for each of the remaining combinations. Across various doses of statins in combination and as monotherapy in all trial populations, significant LDL-c reductions were found with statin-ezetimibe combination (35 trials, of which 94 percent showed 4 to 27 percent additional reduction in LDL-c) and statin-BAS (11 trials, of which 8 trials employing similar doses showed significant, 8 to16 percent, additional reductions favoring	Yes Yes Yes Yes Yes	No No No No No	

combination). With two statin-omega-3 trials, monotherapy was superior. Indeterminate efficacy was noted for the few statin-fibrate and statin-niacin trials. **HDL-c.** There is lack of evidence permitting meaningful conclusions from trials comparing a combination with higher dose of statin monotherapy in populations requiring intensive treatment.	Yes	No	
In trials comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, there was evidence of 1.5 percent increment in HDL-c favoring statin-ezetimibe (15 trials) and statin-fibrate combination therapy, and of no significant difference between monotherapy and statin-BAS combination (four trials). Insufficient evidence compared statin-niacin and statin-omega-3 combination with monotherapy in this population.	Yes	No	
When trials were not restricted to populations in need of intensive treatment, no significant difference in change in HDL-c was noted for simvastatin in combination with ezetimibe vs. higher doses of simvastatin alone (five trials). Evidence from a single trial favored statin-niacin combination, and showed no difference between statin-fibrate and monotherapy. No consistent effect was noted for the statin-ezetimibe combination across diverse trial populations employing various statins and doses. However, across various statins and doses in all populations, significant advantages of the statin-omega-3 and statin-fibrate combinations were noted for HDL-c increment when compared with monotherapy (three trials each), while no significant difference was noted for the statin-BAS combination (nine trials). Five of the six statin-niacin trials favored combination, the exception being the one trial that employed high-dose rosuvastatin in both treatments. **Total cholesterol:HDL-c ratio**. When comparing a	Yes	No	

specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either absent or based on single-trial data, precluding robust conclusions across any combination therapy. A single ezetimibe trial compared lower dose simvastatin in combination vs. higher dose of simvastatin monotherapy in participants requiring intensive lipid-lowering therapy; results favored the combination therapy, demonstrating 14 percent additional reduction. When comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, additional data were available. Significant additional reductions of 3 to 20 percent favoring statin-ezetimibe combination therapy were noted in all 10 trials, with substantial heterogeneity precluding meta-analysis. Evidence was neutral for the statin-fibrate combination (two trials). For other combinations, evidence was either insufficient or absent. Across all available populations, evidence comparing a lower statin dose in combination with a higher dose as monotherapy demonstrated no significant difference between statin-ezetimibe combination and monotherapy. Evidence was insufficient for statin-fibrate combination. Across various statins and doses in all trial populations, 20 statin-ezetimibe trials were not meta-analyzed because of substantial heterogeneity; however, combination treatment was significantly favored in all but one trial. Evidence favored statin-omega combination, did not show a difference for statin-fibrate, was insufficient for statin-niacin, and was totally absent for statin-BAS.ES-8 **Measures of atherosclerosis.** Carotid intimal media thickness (IMT) can be measured by ultrasound and correlates with the presence of atherosclerotic plaque and vascular risk factors. Previous research has shown that statin treatment reduces the progression of this marker. Two trials were available that compared mean change from baseline in the IMT with combination therapy compared to	Yes Yes	No No	

statin monotherapy. One trial of 642 evaluable participants requiring intensive lipid lowering compared simvastatin plus ezetimibe with identical-dose simvastatin monotherapy and yielded indeterminate results. Another trial of 149 evaluable participants requiring intensive lipid-lowering therapy and using mixed statins with niacin and as monotherapy also demonstrated indeterminate results. **Adherence and harm.** For the comparison of a specific statin in combination with a higher dose of its monotherapy across all trial populations, insufficient evidence was available for all combinations except statin-ezetimibe, which showed no significant differences between treatments for the outcomes of withdrawal due to adverse events and liver toxicity (defined as AST/ALT above three times the upper limit of normal). Most trials had a short duration of treatment and followup. Conclusions summarized below pertain to the comparisons of various statins and doses in combination with various statin monotherapies in all trial populations. Early withdrawal due to adverse events was more likely for the combination of statin plus niacin than for statin therapy alone (10 trials with an average duration of 24 weeks). No significant difference was noted for other combinations. Compared with statin monotherapy, more participants developed at least one adverse event with statin-BAS combination (four trials). Inconsistent results were obtained when statin-niacin combination was compared with statin monotherapy. However, three of six trials showed significantly more participants experiencing adverse events with combination than with monotherapy. Available evidence did not indicate significant differences between participants developing AST/ALT above 3 times the upper limit of normal and/or hepatitis, CPK above 10 times the upper limit of normal, or myalgia for a comparison of any combination with statin monotherapy.			

In addition, no participant developed rhabdomyolysis in any of the 27 RCTs investigating the five statin combination therapies, 85 percent of which were short term. No significant difference in treatment adherence was noted for statin-ezetimibe and statin-niacin combinations compared to monotherapy. The statin-BAS trials could not be meta-analyzed due to inconsistent and unexplained direction and magnitude of effects on adherence across five trials.			
Key Question 3. Benefits and Harms Within Subgroups of Patients			
Participants with diabetes mellitus. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy for any relevant outcomes. Across various statin doses in combination and monotherapy, no evidence was available for statin-niacin, statin-BAS, and statin-omega-3 combinations. Compared with statin monotherapy, the statin-ezetimibe combination allowed more participants with diabetes to reach ES-9 ATP III LDL-c goals when monotherapy was of similar statin dose and potency to combination statin (very low quality of evidence) and allowed greater additional reductions in LDL-c, ranging from 4 to 26 percent; TC:HDL-c ratio, 3 to 17 percent; and non-HDL-c, 4 to 24 percent. There was inconsistent evidence for a change in HDL-c between combination and monotherapy treatments. Meta-analysis of two statin-fibrate trials demonstrated no significant difference between treatments for LDL-c reduction, but a significant increase in HDL-c of 5 percent favored the combination. There was insufficient evidence on statin-fibrate combination for other outcomes in participants with diabetes mellitus, including one trial that examined mean percentage reduction in triglyceride in 164 participants, with additional mean reduction of 14 percent favoring combination therapy. Due to the rarity of events,	Yes Yes Yes	No. But the reduced risk and progression of retinopathy and albuminuria (ie. microvascular disease) in patients with type 2 diabetes mellitus in the ACCORD-EYE study is important to note. No No. But I think the sub-group analysis of patients with high triglycerides and low HDL-C showing benefit of adding fenofibrate to simvastatin is important to note	See AIM-HIGH study quoted above for niacin added to statin but it was not in a diabetic population See ACCORD-LIPID sub-study above.

evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and evidence for vascular death was absent across all combinations using various statin doses. **Participants with established vascular disease**. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes in individuals with pre-existing vascular disease. Across various statin doses in combination and monotherapy, there was insufficient evidence examining the statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations with respect to statin monotherapy. Compared with statin monotherapy, statin-ezetimibe combination therapy allowed more participants to reach ATP III LDL-c goals and to reach 9 to 27 percent additional reduction in LDL-c. No significant difference was noted for change in HDL-c for this combination, and evidence was insufficient for TC:HDL-c ratio. Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and not estimable for vascular death from one short-term statin-niacin trial registering no event. **Participants with baseline LDL-c of 190 mg/dL or above**. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes. Across various statin doses in combination and monotherapy, no evidence examined the statin-fibrate, statin-niacin, and statin-omega-3 combinations. Compared	Yes Yes Yes	No No No	

with statin monotherapy, the statin-ezetimibe combination allowed 17 percent additional reductions in LDL-c. Insufficient evidence for this combination was available for other outcomes. No significant difference was noted for change in HDL-c with statin-BAS combination, and evidence was inconsistent for a reduction in LDL-c. Insufficient evidence for this combination was available for other outcomes. **Participants with cerebrovascular disease, females, participants of 80 years of age or older, participants of African descent, participants of Asian descent, and Hispanics.** No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females. However, one large 5-year trial investigating various statins in both treatments among 18,645 Asians resulted in low-quality evidence that there was no significant difference between statin-omega-3 combination and statin monotherapy for the outcome of all-cause mortality.			
CER=comparative effectiveness review; MI=myocardial infarction; LDL=low density lipids; HDL=high density lipids; BAS=bile acid sequestrant; ATP=Adult Treatment Panel; AST= aspartate aminotransferase; ALT= alanine aminotransferase; TC=total cholesterol; AMT=Carotid intimal media thickness			

Comparative Effectiveness of Lipid-Modifying Agents

AHRQ Publication No. 09-EHC024-EF September 2009

Access to full report: http://www.ncbi.nlm.nih.gov/books/NBK43220/

Clinical expert name: Dr. Sharma

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1. Long-Term Benefits and Serious Adverse Events			
There are several important limitations in the evidence regarding long-term clinical outcomes. Most of the evidence originates from short-term studies aimed at biochemical measures and therefore is insufficient for the clinical events of interest, including the occurrence of MI, stroke, or death. In trials of combination therapy, the monotherapy comparator arms rarely explored higher-dose statins or were not performed in individuals requiring intensive lipid lowering. Due to these limitations in the available data, we present first our results based on the available evidence for the group requiring intensive lipid lowering when combination treatment is compared to a higher dose of a statin, and then provide a broader perspective using available data in all risk groups comparing combination therapy to any monotherapy statin dose. **All-cause mortality.** The quality of evidence was very low for all available comparisons of combinations and monotherapy reported below. For individuals requiring intensive therapy, limited	No	The AIM-High Investigators NEJM 2011; 365: 2255-2267	**General Comment:** There have been several new large trials published in this area since the report was written. They contribute significantly more data on both surrogate outcomes (lipid levels) and clinical outcomes including MI, stroke and death. In addition due to the large numbers of participants there is significantly more data on safety outcomes. In some instances the direction of the effect

evidence was available for statin combinations with ezetimibe and fibrates compared to higher doses of statins. In the two statin-ezetimibe combination trials, no deaths occurred in either the combination or the statin monotherapy group, precluding a comparative analysis of mortality. A single trial with a statin-fibrate combination showed no difference in mortality compared with a higher dose statin. Trials comparing combination therapy with statin monotherapy that were not limited to individuals requiring intensive lipid lowering and did not necessarily compare combination therapy with a higher dose of statin monotherapy were examined for an effect on mortality. No significant differences between treatments were observed across any combination, including ES-5statin-omega-3 combination, which was studied in three trials, one of which was a large trial lasting 5 years of 18,645 Asians. **Vascular death.** Treatments aimed at modifying lipids might be expected to lower the rates of death due to vascular diseases such as heart disease and stroke. However, no trials examined this outcome in a high-risk population and compared the combination to a higher statin dose. Across all available trial populations, two trials each of statin-ezetimibe and statin-niacin combinations did not demonstrate a difference in the occurrence of rare vascular deaths. The quality of evidence was very low for evidence pertaining to both combinations. **Other clinical outcomes.** For the outcomes of reduction of MI or stroke or avoidance of revascularization procedures on the carotid or coronary vessels, no evidence comparing combination therapy with a higher dose of statin was available. Evidence comparing various doses of statin-ezetimibe, statin-fibrate, statin-niacin, and statin-BAS			has not changed but the quantity and quality of the evidence significantly impacts on the precision of the conclusions. AIM-High comprised 3414 participants on simva +/- niacin clinical events and death were outcomes. Increase in stroke seen in treatment group

combinations with statin monotherapy was available from few trials registering rare events, and no significant difference was detected. One large statin-omega-3 trial of 18,645 Asians demonstrated no significant difference between treatments for the outcomes of nonfatal MI, hemorrhagic stroke, ischemic stroke, and all stroke over a period of 5 years. **Serious adverse events.** The quality of evidence was very low for all available combination and monotherapy comparisons. Evidence pertained to all available trial populations and not specifically those in need of intensive treatment. Evidence comparing a combination with a higher dose of statin monotherapy was available only for the statin-ezetimibe combination. Three trials with a maximum duration of 24 weeks demonstrated no difference in the rate of serious adverse events. Overall, 5 percent of participants had an event. When various doses and statin types in combinations were compared with statin monotherapy, no significant differences were noted across all combinations, including evidence that combined 27 statin-ezetimibe trials with over 13,000 participants. Absolute rates of serious adverse events varied between 2 and 4 percent. Even across all combinations, no differences were detected when analyses were restricted to the few long-term trials of 24 to 52 weeks duration. **Cancer.** Evidence pertained to all available trial populations and not only those in need of intensive treatment. Some data were available for individuals at any risk level and statin dose. One 5-year omega-3 trial of 18,645 participants demonstrated no significant difference in the incidence of cancer, with an overall rate of 3 percent. With two 24-48-week statin-ezetimibe trials of 971 participants, the rate of incident cancer was 1 percent, with no significant difference between			

treatments. Cancer was too rare in a single small statin-niacin trial to permit any conclusion. No evidence was available for statin-fibrate and statin-BAS combinations. While the available data do not suggest an increased incidence of cancer with ezetimibe or omega-3 combinations, the power to detect small differences in the rates of conditions, such as cancer which may have a long latency prior to presentation, is limited given the current data			
Key Question 2. LDL-c Targets, Short-Term Side Effects, Tolerability, and Adherence			
Surrogate markers are biological markers that are linked to the occurrence of disease and used as targets for therapy. The NCEP ATP report sets treatment goals for various risk categories. In this report, we examine the proportion of individuals attaining the LDL-c goals set by the ATP III panel, the effect on LDL-c and HDL-c levels, the total cholesterol:HDL-c ratio, and markers of atherosclerosis. **Participants attaining ATP III LDL-c goals.** The available evidence is of very low quality for all comparisons of combination with monotherapy. For individuals requiring intensive therapy, two trials employing fixed dose or titrations could be statistically combined. Compared with a higher dose statin alone, statin-ezetimibe combination demonstrated a greater probability of reaching treatment goals. A single trial using a statin-fibrate combination demonstrated no significant difference in the number of participants reaching goals compared to a higher dose statin. No evidence comparing higher dose statin monotherapy with any of the remaining combinations was available for participants requiring intensive treatment. Substantially more information was available for statin-ezetimibe combination therapy in which the treatment comparison was not necessarily a higher dose of statin. In 88 percent of 18 trials conducted in a population in need	No	Additional data provided by trials cited in other Key Questions on LDL-c targets, tolerability and adherence.	

of intensive treatment, combination therapy was more likely than statin monotherapy to help participants reach LDL-c targets. Likewise, 96 percent of 23 trials favored the statin-ezetimibe combination when all trial populations using various statins as the two treatments were included. No evidence was available for the statin-omega-3 combination. Sparse evidence precluding meaningful conclusions was identified for statin-fibrate (two trials), statin-niacin (one trial), and statin-BAS (one trial) combinations across various doses and populations. **LDL-c.** When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either insufficient or absent for statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations. Scant evidence from two statin-ezetimibe trials was not statistically combined because of heterogeneity, but both trials indicated significant additional reductions of 10 to 20 percent favoring statin-ezetimibe combination therapy over monotherapy. More data were observed for individuals requiring intensive therapy when combinations were compared with any dose of statin. Substantial heterogeneity precluded statistical analysis of 18 statin-ezetimibe and 4 statin-BAS trials. However, all statin-ezetimibe trials favored combination treatment, with mean additional reductions of 4 to 27 percent. Inconsistent results were found for statin-BAS trials, while evidence was insufficient for statin-niacin, statin-BAS, and statin-omega-3 combinations. Across all trial populations, when lower doses of statins in combination were compared with higher doses of the same statin monotherapy, significant additional LDL-c reductions of 3 to 20 percent were observed with statin-ezetimibe combinations (six trials); however, heterogeneity precluded a statistical estimate. Evidence			

was insufficient or absent for each of the remaining combinations. Across various doses of statins in combination and as monotherapy in all trial populations, significant LDL-c reductions were found with statin-ezetimibe combination (35 trials, of which 94 percent showed 4 to 27 percent additional reduction in LDL-c) and statin-BAS (11 trials, of which 8 trials employing similar doses showed significant, 8 to16 percent, additional reductions favoring combination). With two statin-omega-3 trials, monotherapy was superior. Indeterminate efficacy was noted for the few statin-fibrate and statin-niacin trials. **HDL-c.** There is lack of evidence permitting meaningful conclusions from trials comparing a combination with higher dose of statin monotherapy in populations requiring intensive treatment. In trials comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, there was evidence of 1.5 percent increment in HDL-c favoring statin-ezetimibe (15 trials) and statin-fibrate combination therapy, and of no significant difference between monotherapy and statin-BAS combination (four trials). Insufficient evidence compared statin-niacin and statin-omega-3 combination with monotherapy in this population. When trials were not restricted to populations in need of intensive treatment, no significant difference in change in HDL-c was noted for simvastatin in combination with ezetimibe vs. higher doses of simvastatin alone (five trials). Evidence from a single trial favored statin-niacin combination, and showed no difference between statin-fibrate and monotherapy.			

No consistent effect was noted for the statin-ezetimibe combination across diverse trial populations employing various statins and doses. However, across various statins and doses in all populations, significant advantages of the statin-omega-3 and statin-fibrate combinations were noted for HDL-c increment when compared with monotherapy (three trials each), while no significant difference was noted for the statin-BAS combination (nine trials). Five of the six statin-niacin trials favored combination, the exception being the one trial that employed high-dose rosuvastatin in both treatments. **Total cholesterol:HDL-c ratio**. When comparing a specific statin in combination with a higher dose statin in populations requiring intensive treatment, evidence was either absent or based on single-trial data, precluding robust conclusions across any combination therapy. A single ezetimibe trial compared lower dose simvastatin in combination vs. higher dose of simvastatin monotherapy in participants requiring intensive lipid-lowering therapy; results favored the combination therapy, demonstrating 14 percent additional reduction. When comparing various statins and doses in combination with various statin monotherapies in populations requiring intensive treatment, additional data were available. Significant additional reductions of 3 to 20 percent favoring statin-ezetimibe combination therapy were noted in all 10 trials, with substantial heterogeneity precluding meta-analysis. Evidence was neutral for the statin-fibrate combination (two trials). For other combinations, evidence was either insufficient or absent. Across all available populations, evidence comparing a lower statin dose in combination with a higher dose as monotherapy demonstrated no significant difference between statin-ezetimibe combination and monotherapy. Evidence was insufficient for statin-fibrate combination.			

Across various statins and doses in all trial populations, 20 statin-ezetimibe trials were not meta-analyzed because of substantial heterogeneity; however, combination treatment was significantly favored in all but one trial. Evidence favored statin-omega combination, did not show a difference for statin-fibrate, was insufficient for statin-niacin, and was totally absent for statin-BAS.ES-8 **Measures of atherosclerosis.** Carotid intimal media thickness (IMT) can be measured by ultrasound and correlates with the presence of atherosclerotic plaque and vascular risk factors. Previous research has shown that statin treatment reduces the progression of this marker. Two trials were available that compared mean change from baseline in the IMT with combination therapy compared to statin monotherapy. One trial of 642 evaluable participants requiring intensive lipid lowering compared simvastatin plus ezetimibe with identical-dose simvastatin monotherapy and yielded indeterminate results. Another trial of 149 evaluable participants requiring intensive lipid-lowering therapy and using mixed statins with niacin and as monotherapy also demonstrated indeterminate results. **Adherence and harm.** For the comparison of a specific statin in combination with a higher dose of its monotherapy across all trial populations, insufficient evidence was available for all combinations except statin-ezetimibe, which showed no significant differences between treatments for the outcomes of withdrawal due to adverse events and liver toxicity (defined as AST/ALT above three times the upper limit of normal). Most trials had a short duration of treatment and followup. Conclusions summarized below pertain to the comparisons of various statins and doses in combination with various statin monotherapies in all trial populations.			

Early withdrawal due to adverse events was more likely for the combination of statin plus niacin than for statin therapy alone (10 trials with an average duration of 24 weeks). No significant difference was noted for other combinations. Compared with statin monotherapy, more participants developed at least one adverse event with statin-BAS combination (four trials). Inconsistent results were obtained when statin-niacin combination was compared with statin monotherapy. However, three of six trials showed significantly more participants experiencing adverse events with combination than with monotherapy. Available evidence did not indicate significant differences between participants developing AST/ALT above 3 times the upper limit of normal and/or hepatitis, CPK above 10 times the upper limit of normal, or myalgia for a comparison of any combination with statin monotherapy. In addition, no participant developed rhabdomyolysis in any of the 27 RCTs investigating the five statin combination therapies, 85 percent of which were short term. No significant difference in treatment adherence was noted for statin-ezetimibe and statin-niacin combinations compared to monotherapy. The statin-BAS trials could not be meta-analyzed due to inconsistent and unexplained direction and magnitude of effects on adherence across five trials.			
Key Question 3. Benefits and Harms Within Subgroups of Patients			
Participants with diabetes mellitus. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with a higher dose of statin monotherapy for any relevant outcomes.	No	The ACCORD Study Group NEJM 2010;362: 1563-74	N=5518 DM with endpoints of MI, Stroke, death over 4.7 yrs. (simva+fenofibrate vs

Across various statin doses in combination and monotherapy, no evidence was available for statin-niacin, statin-BAS, and statin-omega-3 combinations. Compared with statin monotherapy, the statin-ezetimibe combination allowed more participants with diabetes to reach ES-9 ATP III LDL-c goals when monotherapy was of similar statin dose and potency to combination statin (very low quality of evidence) and allowed greater additional reductions in LDL-c, ranging from 4 to 26 percent; TC:HDL-c ratio, 3 to 17 percent; and non-HDL-c, 4 to 24 percent. There was inconsistent evidence for a change in HDL-c between combination and monotherapy treatments. Meta-analysis of two statin-fibrate trials demonstrated no significant difference between treatments for LDL-c reduction, but a significant increase in HDL-c of 5 percent favored the combination. There was insufficient evidence on statin-fibrate combination for other outcomes in participants with diabetes mellitus, including one trial that examined mean percentage reduction in triglyceride in 164 participants, with additional mean reduction of 14 percent favoring combination therapy. Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and evidence for vascular death was absent across all combinations using various statin doses. **Participants with established vascular disease**. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes in individuals with pre-existing vascular disease. Across various statin doses in combination and		Baigent C et al Lancet Vol 377, issue 9784 : 2181-2192	simva monotherapy) N=9270 (chronic kidney disease) endpoints of stroke, MI death (simva+/- ezetimibe)

monotherapy, there was insufficient evidence examining the statin-fibrate, statin-niacin, statin-BAS, and statin-omega-3 combinations with respect to statin monotherapy. Compared with statin monotherapy, statin-ezetimibe combination therapy allowed more participants to reach ATP III LDL-c goals and to reach 9 to 27 percent additional reduction in LDL-c. No significant difference was noted for change in HDL-c for this combination, and evidence was insufficient for TC:HDL-c ratio. Due to the rarity of events, evidence was indeterminate and of very low quality for a difference in all-cause mortality with six statin-ezetimibe and one statin-fibrate trial, and not estimable for vascular death from one short-term statin-niacin trial registering no event. **Participants with baseline LDL-c of 190 mg/dL or above**. Absent or insufficient evidence of very low quality precluded meaningful conclusions regarding comparisons of a lower dose of a statin in any of the five combination therapies with higher dose statin monotherapy for any relevant outcomes. Across various statin doses in combination and monotherapy, no evidence examined the statin-fibrate, statin-niacin, and statin-omega-3 combinations. Compared with statin monotherapy, the statin-ezetimibe combination allowed 17 percent additional reductions in LDL-c. Insufficient evidence for this combination was available for other outcomes. No significant difference was noted for change in HDL-c with statin-BAS combination, and evidence was inconsistent for a reduction in LDL-c. Insufficient evidence for this combination was available for other outcomes. **Participants with cerebrovascular disease, females, participants of 80 years of age or older, participants of**	No		Additional evidence for females in AIM-High cited above. Other trials also include subgroup analysis by sex and, often age.

African descent, participants of Asian descent, and Hispanics. No evidence was available for participants with cerebrovascular disease and those age 80 years and over. Sparse evidence of very low quality, precluding meaningful conclusions, was available in subgroups of participants of different ethnic origins and females. However, one large 5-year trial investigating various statins in both treatments among 18,645 Asians resulted in low-quality evidence that there was no significant difference between statin-omega-3 combination and statin monotherapy for the outcome of all-cause mortality.			
CER=comparative effectiveness review; MI=myocardial infarction; LDL=low density lipids; HDL=high density lipids; BAS=bile acid sequestrant; ATP=Adult Treatment Panel; AST= aspartate aminotransferase; ALT= alanine aminotransferase; TC=total cholesterol; AMT=Carotid intimal media thickness			

Comparative Effectiveness of Lipid-Modifying Agents

AHRQ Publication No. 09-EHC024-EF September 2009

Access to full report: http://www.ncbi.nlm.nih.gov/books/NBK43220/

Clinical expert name: Dr. Ashfaq Shuaib

This expert did not provid his answers in the above table but instead wrote, "I am unaware of any new studies specifically evaluating statins in stroke patients. To my knowledge there are no studies in cardiac literature that have looked specifically at stroke outcomes….however I don't always read this literature well. My answer to all the questions in your attachment would be 'NO'".

Appendix E: FDA Alerts

EFFECTIVE HEALTHCARE REPORTS - FDA ALERTS

FDA Activity for the Period of November 1-30, 2011

Assigned EPC	Ottawa
Sent	Yes
Date Sent to EPC	12/12/2011
EHC Surveillance Activity Date	11/25/2011
Intervention	Drug
Drug/Product Information	Simvastatin
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/2009
Link to Report	http://www.effectivehealthcare.ahrq.gov/ehc/products/11/171/rdyfin-typofixed4-12-2010.pdf
Source of Notification	FDA
Notification Type	Label Change
Notification Content	WARNINGS AND PRECAUTIONS *Myopathy/Rhabdomyolysis* • Zocor therapy should be discontinued if markedly elev CPK levels occur or myopathy is diagnosed or suspec • Amiodarone added to TABLE 1 *Liver Dysfunction* • There have been rare postmarketing reports of fatal a non-fatal hepatic failure in patients. *Endocrine Function* • Increases in HbA1c and fasting serum glucose levels been reported. ADVERSE REACTIONS *Post-Marketing Experience* • fatal and non-fatal hepatic failure (added) • There have been rare postmarketing reports of cogniti

	impairment. PATIENT COUNSELING INFORMATION *Liver Enzymes* • All patients treated with ZOCOR should be advised to report promptly any symptoms that may indicate liver injury.
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208610.htm
ECRI Institute Comments/Rationale	Key Questions 1 and 2. Notification on adverse events.
Ongoing Safety Review	None.

EFFECTIVE HEALTHCARE REPORTS - FDA ALERTS

FDA Activity for the Period of June 1-30, 2011

Assigned EPC	Ottawa
Sent	Yes
Date Sent to EPC	07/10/11
EHC Surveillance Activity Date	06/25/11
Intervention	Drug
Drug/Product Information	Simvastatin
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/09
Link to Report	http://effectivehealthcare.ahrq.gov/ehc/products/11/171/reptbodyfin-typofixed4-12-2010.pdf
Source of Notification	FDA
Notification Type	Drug Safety Communication
Notification Content	Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug.
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258384.htm
ECRI Institute Comments/Rationale	Key Questions 1 and 2. Notification on adverse events.
Ongoing Safety Review	None.

EFFECTIVE HEALTHCARE REPORTS - FDA ALERTS

FDA Activity for the Period of May 1-31, 2011

Assigned EPC	Ottawa
Sent	Yes
Date Sent to EPC	06/15/11
EHC Surveillance Activity Date	05/25/11
Intervention	Drug
Drug/Product Information	Ezetimibe/simvastatin
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/09
Link to Report	http://www.effectivehealthcare.ahrq.gov/ehc/products/11/170/Lipids%20exec%20summ.pdf
Source of Notification	FDA
Notification Type	Label Change
Notification Content	ADVERSE REACTIONS Post-Marketing Experience • erectile dysfunction • interstitial lung disease PATIENT PACKAGE INSERT What are the possible side effects of Vytorin? • Erectile dysfunction • breathing problems including persistent cough and/or shortness of breath or fever WARNINGS and PRECAUTIONS Drug Interactions The benefits of the combined use of VYTORIN with the following drugs should be carefully weighed against the potential risks of combinations: diltiazem. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis • Diltiazem: Do not exceed 10/40 mg Vytorin daily • The combined use of Vytorin in patients at doses higher

	than 10/40 mg daily with diltiazem should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. Myopathy/Rhabdomyolysis • Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with Vytorin coadministered with lipid-modifying doses of niacin containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive Vytorin 10/80 mg coadministered with lipid-modifying doses of niacin-containing products
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208609.htm
ECRI Institute Comments/Rationale	Key Questions 1, 2, and 3 Notification on adverse events specifically among Chinese patients.
Ongoing Safety Review	None.

Assigned EPC	**Ottawa**
Sent	Yes
Date Sent to EPC	06/15/11
EHC Surveillance Activity Date	05/25/11
Intervention	Drug
Drug/Product Information	Niacin extended release/lovastatin
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/09
Link to Report	http://www.effectivehealthcare.ahrq.gov/ehc/products/11/170/Lipids%20exec%20summ.pdf
Source of Notification	FDA
Notification Type	Label Change
Notification Content	ADVERSE REACTIONS • The following adverse reactions are being added: depression, peripheral nerve palsy, dermatomyositis,

	progression of cataracts.
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm243486.htm
ECRI Institute Comments/Rationale	Key Questions 1 and 2 Notification on adverse events.
Ongoing Safety Review	None.

Assigned EPC	**Ottawa**
Sent	Yes
Date Sent to EPC	06/15/11
EHC Surveillance Activity Date	05/25/11
Intervention	Drug
Drug/Product Information	Niacin extended release/simvastatin
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/09
Link to Report	http://www.effectivehealthcare.ahrq.gov/ehc/products/11/170/Lipids%20exec%20summ.pdf
Source of Notification	FDA
Notification Type	Label Change
Notification Content	ADVERSE REACTIONS Postmarketing Experience • Erectile dysfunction, depression, interstitial lung disease, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), muscle cramps, vomiting, malaise
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm246724.htm
ECRI Institute Comments/Rationale	Key Questions 1 and 2 Notification on adverse events.
Ongoing Safety Review	None.
Assigned EPC	Ottawa

Sent	Yes
Date Sent to EPC	06/15/11
EHC Surveillance Activity Date	05/25/11
Intervention	Drug
Drug/Product Information	Rosuvastatin calcium
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/09
Link to Report	http://www.effectivehealthcare.ahrq.gov/ehc/products/11/170/Lipids%20exec%20summ.pdf
Source of Notification	FDA
Notification Type	Label Change
Notification Content	Postmarketing Experience • Depression and sleep disorders (including insomnia and nightmares) WARNINGS AND PRECAUTIONS Skeletal Muscle Effects • Cases of myopathy and rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with HMG-CoA reductase inhibitors, including Crestor. These risks can occur at any dose level, but are increased at the highest dose (40 mg). DRUG INTERACTIONS • Cyclosporine: Combination increases rosuvastatin exposure. Limit Crestor dose to 5 mg once daily. • Lopinavir/Ritonavir or atazanavir/ritonavir: Combination increases rosuvastatin exposure. Limit Crestor dose to 10 mg once daily
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm200635.htm
ECRI Institute Comments/Rationale	Key Questions 1 and 2 Notification on adverse events.
Ongoing Safety Review	None.

Assigned EPC	Ottawa
Sent	Yes
Date Sent to EPC	06/15/11
EHC Surveillance Activity Date	05/25/11
Intervention	Drug
Drug/Product Information	Simvastatin
EHC Report Likely To Be Impacted	Comparative Effectiveness of Lipid-Modifying Agents
Population	Patients (Very high-risk, high-risk and those with LDL-c ≥ 190 mg/dL)
Status of Report	Final
Publication Date	09/01/09
Link to Report	http://www.effectivehealthcare.ahrq.gov/ehc/products/11/170/Lipids%20exec%20summ.pdf
Source of Notification	FDA
Notification Type	Label Change
Notification Content	ADVERSE REACTIONS Postmarketing Experience • erectile dysfunction and interstitial lung disease WARNINGS and PRECAUTIONS Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis • Diltiazem: Do not exceed 40 mg simvastatin daily • The combined use of simvastatin in patients receiving diltiazem should not exceed 40 mg daily unless the clinical benefit is likely to outweigh the increased risk of myopathy. • Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with simvastatin coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. DRUG INTERACTIONS Amiodarone, Verapamil, or Diltiazem • The risk of myopathy/rhabdomyolysis is increased by concomitant administration of amiodarone, verapamil, or

	diltiazem with higher doses of simvastatin
Link to Notification	http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm208610.htm
ECRI Institute Comments/Rationale	Key Questions 1, 2, and 3 Notification on adverse events specifically among Chinese patients.
Ongoing Safety Review	None.

FDA Drug Safety Communication:Review update of Trilipix (fenofibric acid) and the ACCORD Lipid trial

Safety Announcement
Additional Information for Patients
Additional Information for Healthcare Professionals
Data Summary

Safety Announcement

[11-9-2011] The U.S. Food and Drug Administration (FDA) is informing the public that the cholesterol-lowering medicine Trilipix (fenofibric acid) may not lower a patient's risk of having a heart attack or stroke. This is based on data from the **A**ction to **C**ontrol **C**ardiovascular **R**isk in **D**iabetes (ACCORD) Lipid trial, which evaluated the efficacy and safety of fenofibrate plus simvastatin combination therapy versus simvastatin alone in patients with type 2 diabetes mellitus (see Data Summary below). FDA reviewed this trial as part of its ongoing investigation of the safety and efficacy of Trilipix.

Information from the trial has been added to the *Important Limitations of Use* and *Warnings and Precautions* sections of the Trilipix physician label and to the patient Medication Guide.

Healthcare professionals should consider the benefits and risks of Trilipix when deciding to prescribe the drug to patients. Patients should contact their healthcare professional if they have any questions or concerns about Trilipix.

In the ACCORD Lipid trial, there was no significant difference in the risk of experiencing a major adverse cardiac event between the group treated with fenofibrate plus simvastatin compared with simvastatin alone. In addition, a subgroup analysis showed that relative to treatment in men, there was an increase in the risk for major adverse cardiac events in women receiving the combination therapy versus simvastatin alone. The clinical significance of this subgroup finding is unclear, as this finding was not observed in a separate large randomized controlled clinical trial of fenofibrate versus placebo.

Facts about Trilipix (fenofibric acid)

- A prescription medicine used to treat cholesterol in the blood by lowering low-density lipoprotein (LDL) cholesterol ("bad cholesterol"), and increasing the high-density lipoprotein (HDL) cholesterol ("good cholesterol").
- Can be used to lower very high levels of fat (triglycerides) in the blood to help reduce the risk for pancreatitis.
- Can be used in combination with other cholesterol-lowering medicines called statins in patients at high risk for cardiovascular disease.

Based on results from the ACCORD Lipid trial and other clinical trials of drugs similar to Trilipix, FDA is requiring the manufacturer of Trilipix to conduct a clinical trial to evaluate the cardiovascular effects of Trilipix in patients at high risk for cardiovascular disease who are already taking statins.

FDA had previously communicated to the public about the ACCORD Lipid trial in a Statement to Healthcare Professionals on March 15, 2010. The results of this trial were later discussed at the FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting, held on May 19, 2011.